Determination Of Variation In Flow Property of Different Formulas Of Zinc Stearate Along With Amlodipine And Propranolol

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

DECLARATION BY THE CANDIDATE

I, **Jarrin Rashid**, hereby declare that this dissertation, entitled "**Determination of variation in flow property of different formulas of Zn stearate along with Amlodipine and Propranolol**" is an authentic and genuine thesis project carried out by me under the guidance of **Mr Mohammed Faisal Bin Karim,** Senior Lecturer, (supervisor) and **Mr MD. Anisur Rahman,** Senior Lecturer, (co supervisor), Department of Pharmacy, East West University, Dhaka.

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CERTIFICATE BY THE SUPERVISOR

This is to certify that the dissertation entitled **"Determination of variation in flow property of different formulas of Zinc stearate along with Amlodipine and Propranolol"** submitted to the Department of Pharmacy, East West University, in partial fulfillment of the requirements for the Degree of Bachelor of Pharmacy, was carried out by **Jarrin Rashid**, **ID No. 2012-1-70-050** under my supervision and no part of this dissertation has been or is being submitted elsewhere for the award of any Degree/Diploma.

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ENDORSEMENT BY THE CHAIRPERSON

This is to certify that the dissertation entitled **"Determination of variation in flow property of different formulas of Zinc stearate along with Amlodipine and Propranolol"** is a genuine research work carried out by **Jarrin Rashid**, under the supervision of **Mr Mohammed Faisal Bin Karim,** Senior Lecturer (supervisor) and **Mr Md. Anisur Rahman,** Senior Lecturer (Co supervisor) from 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 this connection are duly acknowledged.

Prof. Dr. Shamsun Nahar Khan
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Jarrin Rashid

Dedication

This Research Paper is Dedicated
To
My Beloved Parents

ABSTRACT

This work was proposed to determine the flow properties of different set of some important pharmaceutical excipients along with APIs that are most commonly used to search some equations which can predict the flow property of any set of excipients and APIs with different ratio of antiadherent. Different parameters to determine flow property such as Compressibility index, Hausner ratio, and angle of repose were observed for them. Many unique formulas were equipped by choosing various excipients from different classes. Antiadherents were mixed with these prepared formulas in different specific and justified ratio. The prepared mixture in a constant weight was then examined for measuring flow property. I also used APIs to determine the difference in flow property.The values of Carr's index, Hausner ratio and angle of repose were plotted against the percentage ratios of antiadherent. The study showed a linear relationship with different ratios of mixture and flow property measuring parameters. From these graphs the straightline equations for each set of formula were obtained with regression value close to 1 which can be used to predict the flow property of these formula with different ratio of diluents. Moreover the most suitable ratio of specific antiadherent and a specific set of excipients along with APIs were proposed that showed better flow property.

Key words: Carr's Index, Hausner Ratio, Angle of repose, bulk volume, tapped volume, antiadherent.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

Chapter One

INTRODUCTION

1.1 INTRODUCTION

In the pharmaceutical industry uniform flow of powders is one of the most important considerations in formulation development.The aim of the research work was to determine the powder flow property of any set of excipients with different ratio of antiadherents by using different active pharmaceutical ingredients.Powder flow characteristics are determined using different parameters such as bulk density, tapped density, Carr's Index, Hausner Ratio, angle of repose for different mixture of same pharmaceutical excipients and APIs but in different ratio and were able to resolve an equation.We had done this for different mixtures of different excipients and APIs to determine different equations.

The purpose of my research project was to check the variable flow properties of any set of excipients from plotting a standard curve of a particular combination of excipients with APIs.For accurate result the experiment were done for five times and all the guidelines were followed.

1.2 POWDER FLOW PROPERTY

1.2.1 Introduction

Powders are ubiquitous, they can be found in almost every industry. Good flowability of the powders is important in each of these industries. Although there is no single definition for good flowability, it is generally taken to mean that the powder flows reliably without assistance. Blending, transfer, storage, feeding, compaction, and fluidization all depend on good powder flowability. Designing and troubleshooting mass flow hoppers requires the measurement of powder flow. Tabletting operations require excipients with the desired flow, physical and mechanical properties. In the pharmaceutical industry in particular, uniform flow of solid mixtures is one of the most important considerations in solid dosage manufacture.

(Freemantech, 2013)

1.2.2 Importance of learning accurate flow property:

It is really important for 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 require 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 problem (flow impediments, segregation, or any irregular flow etc) will occur. Few methods of assessing powder flow can be time consuming. However the benifits of accurately exemplifying powder flow measurement can far be more important than this venture of time.

- **Developing new product or dosage form:**

A team from product development can assess new excipients, active drugs, formulations, predicting their behaviour prior to inauguration to large scale production.They can also check how new powders (excipients) interacting with existing ingredients. This speed up development time and which minimizes errors during final production. 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 improve blending quality, filling procedures and end product quality.

- **Cost savings of existing product:**

The subtituents of lower cost powders with lower cost powders is a smart approach because the cause of existing product should be driven down. Although this substitutes may be produced to the same specification as the original substance, they may not essentially srore, 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:

Some powders are free flowing while some are cohesive. Powder flow is governed more by physical properties rather than chemical properties. Factors regarding flow property of powders are as follows:

- **Particle size and size distribution:**

Particle size and size distribution of the particles should be such that it will comply with the flow characteristics of the powder. An alteration of particle size may alter the shape of it, eventually the flowability is changed.For example fine particles tend to be more cohesive and therefore less free flowing whereas larger denser particles tend to be more flowing.

- **Particle shape:**

Particle shape is of upmost importance in order to get required flow behaviour.Spherical shape is the best shape which gives maximum flow.Irregular shape may cause bridging in hopper.Small, irregularly shaped powders are generally considered to cause more flow difficulties than large, well rounded particles. In this experiment, the large size particles were grinded in mortar and pastle to provide uniform properties.

- **Moisture:**

The effect of moisture on flowability of particles varies from powder to powder. The particles become cohesive due to moisture absorption. In presence of excessive moisture, the powder shows poor flowability. In this experiment, I have used desiccant in different powder bulk to remove the moisture content from the powder and maximize the flow characteristic of the powders used.

- **Electrostatic effects:**

The charged material show poorer flow than uncharged material. Particles can acquire static charges by grinding, collision, mixing, sieving and moisture. In this experiment, this factor is maintained properly.

- **Powder cohesion and storage compaction:**

When solid remains at rest or stored in a hopper or bin, it can become more cohesive and gives poor flow.

- **Effect of temperature:**

Temperature is a very influential factor for flow property. Higher or lower the temperature can make the powder degrade and also hamper natural flow behavior. So in this experiment the temperature of the laboratory was maintained at room temperature at which the powders generate its natural quality.

(Slideshare, 2013)

1.2.4 Parameters checked during the 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; this part proposes the standardization of test methods that may be valuable during pharmaceutical development. Four commonly described methods for testing powder flow are-

- Angle of repose
- Compressibility index and Hausner ratio
- Bulk density and Tapped density

However, there are numerous variations of these methods, test methodology and operating scheme.

(Pharmacopeia,2013)

1.2.4.1 Angle of repose:

The angle that the plane of contact between two bodies makes with the horizontal when the upper body is just on the point of sliding is called the angle of repose. The angle of repose is the angle which is relative to the horizontal base of the conical pile produced when a granular material is poured on to a horizontal surface. It is also known as the critical angle of repose. The angle of repose can range from 0° to 90°. Lower the angle of repose, better the flow property

(Merriam, 2013)

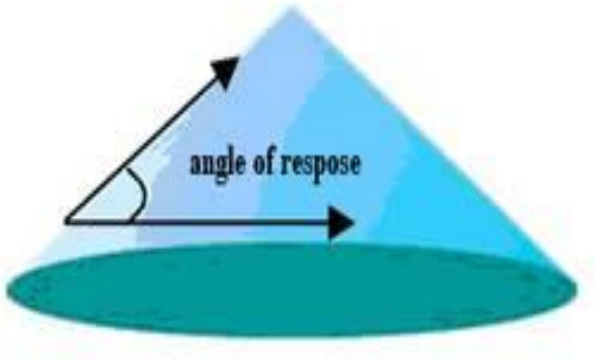

Fig1.1: Angle of repose (Merriam, 2013)

When bulk granular materials are poured onto a horizontal surface, a conical pile will form. The internal angle between the surface of the pile and the horizontal surface is known as the angle of repose and is related to the density, surface area and shapes of the particles, and the coefficient of friction of the material. It also depends on gravity. Material with a low angle of repose forms flatter piles than material with a high angle of repose.
The angle of repose has been used to characterize the flow properties of powders. It is related to interparticulate friction or movement between particles. Results were only considered valid when a symmetrical cone of powder was formed

(Copleyscientific, 2012).

Table 1.1 : Relation between flow properties and angle of repose

Flow properties	Angle of Repose
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Very very poor	>66

Factors that influence the angle of repose:

- Decrease the particle size, higher angle of repose
- Fine particles (up to 15%), increase angle of repose
- Lubricants at low concentration, lower the angle of repose
- Rough and irregular surface, higher angle of repose

(Authorstream , 2013).

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.

Figure 1.2: [Left to right] Measuring angle of repose and a set up of funnel

The angle of repose can be calculated by the following formula:

$$\theta = \tan^{-1} \frac{h}{r}$$

Where h = Height of pile
r = Radius of pile

1.2.4.2Compressibility index and Hausner ratio

1.2.4.2.1 Compressibility Index

The two most commonly used measures of the relative importance of interparticulate interactions are the compressibility index and the Hausner ratio as these are the simplest, fast and popular methods of predicting powder flow characteristics.

The Carr's index also known as Carr's Compressibility Index is an indication of the compressibility of a powder. Compressibility is a measure of the relative volume change of a fluid or solid as a response to a pressure change or stress. It is named after the pharmacologist Charles Jelleff Carr. It measures the relative significance of interparticle interactions.

(Wikianswers, 2013)

1.2.4.2.2Hausner Ratio

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. It is named after the engineer Henry H. Hausner. The Hausner ratio is used in a wide variety of industries as an indication of the flowability of a powder. A Hausner ratio greater than 1.25 is considered to be an indication of poor flowability and less than 1.25 is considered to be an indication of free flowing.

The Carr's index and Hausner Ratio are calculated by the formula below:

$$Compressibility\ Index = 100 \times \left(\frac{V_o - V_f}{V_o} \right)$$

$$Hausner\ Ratio = \frac{V_o}{V_f}$$

Where,
Vo = Bulk volume
Vf = Tapped volume

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.

Table 1.2: Scale of Nature of flow in Carr's Index and Hausner's Ratio Values

Compressibility Index (per cent)	Flow character	Hausner Ratio
1-10	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

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

1.2.4.3Bulk density and Tapped density

1.2.4.3.1 Bulk density:

The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the interparticulate void volume. The bulk density depends on both the density of powder particles and the spatial arrangement of particles in the powder bed. It is expressed in grams per ml (g/ml) or grams per cubic centimeter and the international unit is kilograms per cubic meter as the bulk density is measured in cylinders.
The bulk density of a solid is often very difficult to measure since the slightest disturbance of the bed may result in a new bulk density. The interparticulate interactions that influence the bulking properties of a powder are also the interactions that interfere with powder flow.

A known weight of sample is placed into a measuring cylinder and tapped (manually or mechanically to lower the set of distance) until a consistent volume is reached which corresponds to the maximum packing density of the material.

(Wikianswers, 2013)

1.2.4.3.2 Tapped density:

It is the maximum packing density of a powder (or blend of powders) achieved under the influence of well-defined, externally applied forces. The tapped density is obtained by mechanically tapping a graduated cylinder containing the sample until little further volume change is observed. The minimum packed volume thus achieved depends on a number of factors including particle size distribution, true density, particle shape and cohesiveness due to surface forces including moisture. Therefore, the tap density of a material can be used to predict both its flow properties and its compressibility. (Wikianswers , 2013)

Tapped density is measured by tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped and volume reading was taken until little further volume change is observed. The tapping is achieved by raising the cylinder and allowing it to drop under a specified distance.

(Pharmacopeia, 2013)

The bulk density and tapped density are calculated by formula below:

$$Bulk\ Density(V_b) = \frac{Mass}{Bulk\ Volume} \qquad (1)$$

$$Tapped\ Density(V_t) = \frac{Mass}{TappedVolu\ me} \qquad (2)$$

Fig 1.3: Bulk volume measurement without tapping (A) and Tapped volume measurement after tapping (B)

In free-flowing powders the initial bulk and tapped densities will be more similar than in poor flowing powders which yield greater differences between the two values.

Factors that influence the bulk and tapped 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

(Authorstream , 2013).

1.3 PHARMACEUTICAL EXCIPIENTS

Information available from their website of U.S. Pharmacopeia (Anon.,2010) Excipients are defined as any substances, other than the active drug or product, that have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing of the drug delivery system during its manufacture, protect, support or enhance stability, bioavailability, or patient acceptability, assist in product identification, or enhance any other attribute of the overall safety and effectiveness of the drug delivery system during storage or use.

(Pharmacopeia, 2013)

Drug products contain both drug substance, commonly referred to as active pharmaceutical ingredient (API) and excipients. Reasons for this include the followings:

Ease of administration to the target patient population by the proposed route

- Improved dosing compliance
- Consistency and control of drug bioavailability
- To enable bioavailability
- Improved API stability including protection from degradation
- To ensure a robust and reproducible physical product.

(Mills, 2010)

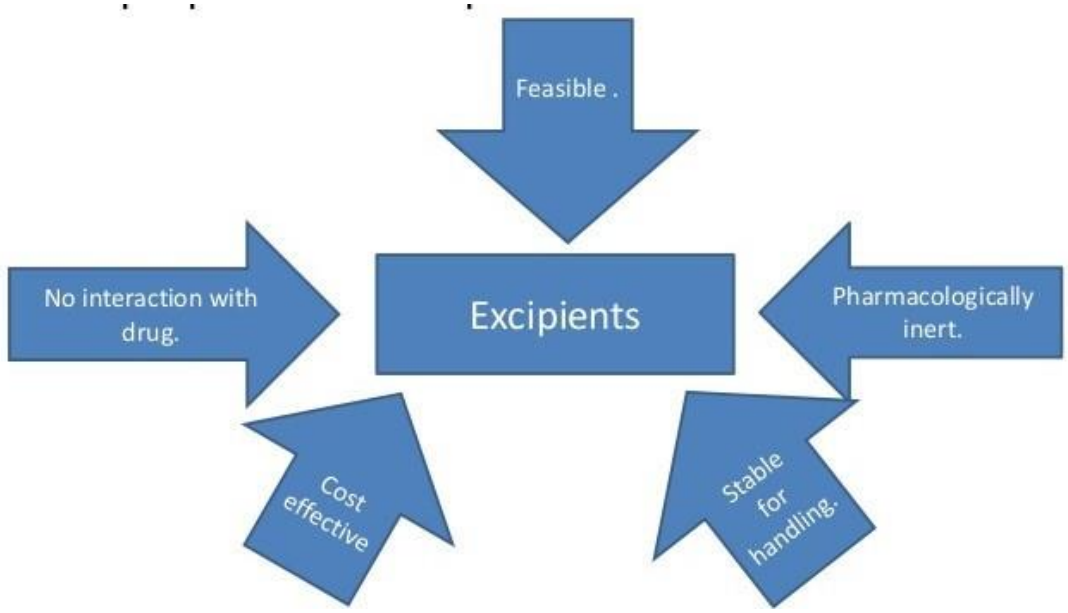

Fig 1.4: Ideal properties of excipients

1.3.1 Types of excipients

Table 1.3:Different types of excipients and their functions

Excipients name	Function
Antiadherent	Used to reduce the adhesion between powders (granules).
Binders	Binders hold the ingredients in a tablet together.
Coatings	Used to prevent the tablet ingredients from detoriation by moisture
Disintegrants	It dissolves when wet causing the tablet to break apart.
Fillers and diluents	They fill out the size of a tablet.
Flavors	It is used to mask the unpleasant test of active ingredients.
Colors	It is used to improve the appearance of a formulation.
Glidants	Glidants promote powder flow by reducing interparticle friction.
Lubricants	Lubricants prevent ingredients from clumping together and from sticking to the tablet punches.
Preservatives	Preservatives preserve the formulation.

1.3.1.1 Antiadherent

Antiadherents are used to reduce the adhesion between the powder (granules) and the punch faces and thus prevent sticking to tablet punches. They are also used to help protect tablets from sticking. Some material have strong adhesive properties towards the metal of punches and dies or the tablet formulation containing excessive moisture which has tendency to result in picking and sticking problem. Therefore antiadherents are added, which prevent sticking to punches and die walls.

Some commonly used antiadherents are as follows: Talc (1 – 5%), stearates like Mg stearate, Zn stearate and corn starch (3 – 10%), Sodium lauryl sulfate (less than 1%), have excellent antiadherent properties.

(Apu, 2010)

1.3.1.2 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.

Common binders include,
Saccharides, gelatins, polyethylene glycol (PEG), starches, cellulose or modified cellulose such as microcrystalline cellulose, hydroxypropylcellulose (HPC), methyl cellulose and cellulose ethers, as well as polyvinylpyrrolidone (PVP).

- Binders are 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.

- Dry binders are added to the powder blend, either after a wet granulation step, or as part of a direct powder compression formula. Examples include cellulose, methyl cellulose, polyvinyl pyrrolidone and polyethylene glycol.

(Excipients, 2013)

1.3.1.3 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.

(Pformulate, 2000)

1.3.1.4 Filers and diluents:

Dilents are also known as bulking agents or fillers. Diluents added to the active ingredient in sufficient quantity to make a reasonably sized tablet. A tablet should at least 50mg and therefore very low dose drugs (diazepam, clonidine hydrochloride) will invariably require a diluent to bring the overall tablet weight to at least 50mg. This agent may not be necessary if dose of drug per tablet is high (e.g. aspirin and certain antibiotics). Usually the range of diluents may vary from 5-80%.

(Apu, 2010)

Fillers or diluents typically also fill out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use.A good filler should typically be inert, compatible with the other components of the formulation, non-hygroscopic, relatively cheap, compactible, and preferably tasteless or pleasant tasting. Plant cellulose (pure plant filler) is popular filler in tablets or hard gelatin capsules. Dibasic calcium phosphate is popular tablet filler. A range of vegetable fats and oils can be used in soft gelatin capsules. Other examples of fillers include: lactose, sucrose, glucose, mannitol, sorbitol, calcium carbonate, and magnesium stearate. Sometimes other noted kinds of excipients are in effect doubling in function as fillers.

(Excipients, 2013)

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.

1.3.1.4.1 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)

1.3.1.4.2Influence 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.

(Apu, 2010)

1.3.1.4.3 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's discoloration of tablets with time.

(Apu, 2010)

1.3.1.5 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.

There are three roles identified with lubricants as follows:

- To decrease friction at the interface between a tablet's surface and the die wall during ejection and reduce wear on punches & dies.
- Prevent sticking to punch faces or in the case of encapsulation, it prevents sticking to machines.
- Enhance product flow by reducing interparticulate friction

Lubricants or glidants for tablet must meet some criteria. They are as follows:

- Low Shear Strength.
- Able to form a durable layer over the surface covered.
- Non-Toxic.
- Chemically inert.
- Unaffected by process variables
- Posses minimal adverse effects on the finished dosage form

(Apu, 2010)

1.3.1.6 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.

(Apu, 2010)

1.3.1.7 Miscellaneous

1.3.1.7.1 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.

1.3.1.7.2 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.

1.3.1.7.3 Surfactants

Wetting agents such as sodium lauryl sulphate may be included, especially if the drug substance is hydrophobic.

1.3.1.7.4 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.

(Apu, 2010)

1.4 SHORT NOTES ON EXCIPIENTS USED IN THE EXPERIMENT

1.4.1 Talc:

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

- Empirical Formula: Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4(OH)_4$. It may contain small, variable amounts of aluminum silicate and iron.

1.4.1.1Functional Category

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Table 1.4 Uses of Talc

Uses	Concentration %
Dusting powder	90.0-99.00
Glidant and tablet lubricant	1.0-10.0
Tablet and capsule diluents	5.0-30.0

1.4.1.2 Applications in Pharmaceutical Formulation or Technology

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent, see Table I,(1–3) although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release, pellets; and as an adsorbent.

In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves. Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder;

Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

(Rowe, Sheskey, Owen, 2005)

1.4.2 Starch:

Starch occurs as an odorless and tasteless, fine, white-colored powder comprising very small spherical or ovoid granules whose size and shape are characteristic for each botanical variety.

- Empirical Formula: $(C_6H_{10}O_5)_n$; Where, n =300–1000.

Starch consists of amylase and amylopectin, two polysaccharides based on α-glucose.

- Molecular weight: 50000–160000

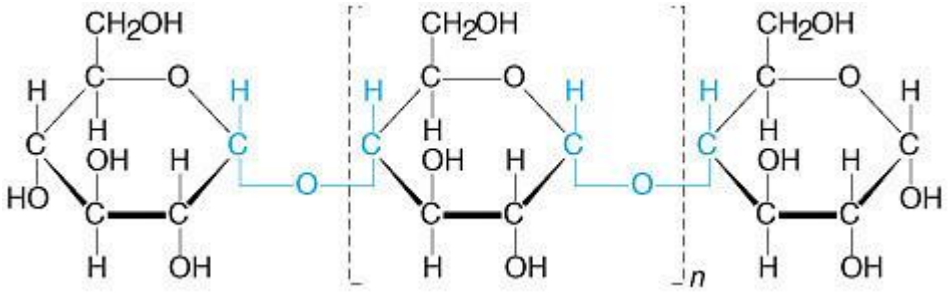

Fig 1.5:Starch (Rowe, Sheskey, Owen, 2005)

1.4.2.1Functional Category

Glidant; tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

1.4.2.2 Applications in Pharmaceutical Formulation or Technology

- Starch is used as an excipient primarily in oral solid-dosage formulations where it is utilized as a binder, diluent, and disintegrant.
- As a diluent, starch is used for the preparation of standardized triturates of colorants or potent drugs to facilitate subsequent mixing or blending processes in manufacturing operations. Starch is also used in dry-filled capsule formulations for volume adjustment of the fill matrix.
- In tablet formulations, freshly prepared starch paste is used at a concentration of 5–25% w/w in tablet granulations as a binder. Selection of the quantity required in a given system is determined by optimization studies, using parameters such as granule friability, tablet friability, hardness, disintegration rate, and drug dissolution rate.
- Starch is one of the most commonly used tablet disintegrants at concentrations of 3–15% w/w. However, unmodified starch does not compress well and tends to increase tablet friability and capping if used in high concentrations. In granulated formulations, about half the total starch content is included in the granulation mixture and the balance as part of the final blend with the dried granulation.
- Starch is also used in topical preparations; for example, it is widely used in dusting powders for its absorbency, and is used as a protective covering in ointment formulations applied to the skin. Starch mucilage has also been applied to the skin as an emollient, has formed the base of some enemas, and has been used in the treatment of iodine poisoning.

(Rowe, Sheskey, Owen, 2005)

1.4.3 Polyethylene glycol (PEG)

Polyethylene glycol (PEG) is a polyether compound with many applications from industrial manufacturing to medicine. It is a high molecular weight polymer of ethylene oxide and is a blend of polymers with different degrees of polymerization. It acts as binder & dry lubricant due to its laminar structure and therefore can be used in the manufacture of pills and tablets for certain pharmaceutical preparations .The natural lubricity, low volatility and water solubility of PEGs make them useful in a wide range of lubricants.

(Dow, 2011)

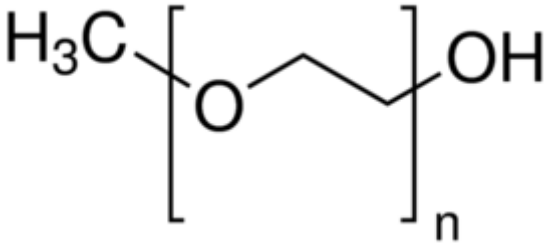

Fig1.6: PEG (Dow, 2011)

1.4.4 Zinc Stearate:

According to United States Pharmacopoeia, 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.

(Pharmacopeia, 2013)

1.4.5 Carboxymethyl cellulose (CMC)

Carboxy methyl cellulose calcium occurs as a white to yellowish-white, hygroscopic, fine powder.

- Empirical Formula: The USP NF 23 describes carboxymethylcellulose calcium as the calcium salt of polycarboxy methyl ether of cellulose.

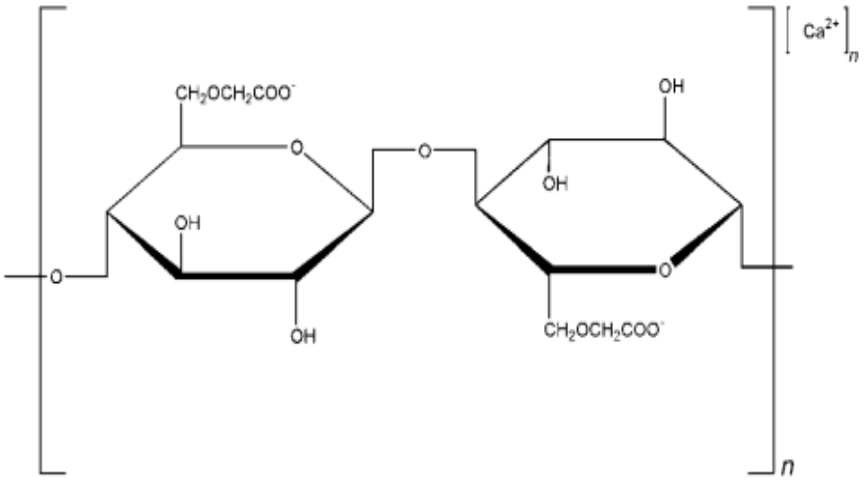

Fig 1.7: Carboxymethyl cellulose (Rowe, Sheskey, Owen, 2005)

1.4.5.1 Functional Category

Stabilizing agent; suspending agent; tablet and capsule disintegrant; viscosity-increasing agent; water-absorbing agent.

1.4.5.2 Uses of Carboxymethyl cellulose calcium

- Tablet binder (5-15)
- Tablet disintegrant (1-15)

1.4.5.3 Applications in Pharmaceutical Formulation or Technology

- The main use of carboxymethylcellulose calcium is in tablet formulations, where it is used as a binder, diluent, and disintegrant. Although carboxymethylcellulose calcium is insoluble in water, it is an effective tablet disintegrant as it swells to several times its original bulk on contact with water. Concentrations up to 15% w/w may be used in tablet formulations; above this concentration, tablet hardness is reduced.
- Carboxymethyl cellulose calcium is also used in other applications similarly to Carboxymethyl cellulose sodium; for example, as a suspending or viscosity increasing agent in oral and topical pharmaceutical formulations. Carboxymethyl cellulose calcium is also used in modern wound dressings for its water absorption, retention and hemostatic properties.

(Rowe, Sheskey, Owen, 2005)

1.4.6 Polyvinyl Pyrrolidone (PVP)

Polyvinyl Pyrrolidone is also known as Povidone (USP), 1-vinyl-2-pyrrolidinone polymer. Povidone or PVP occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder.

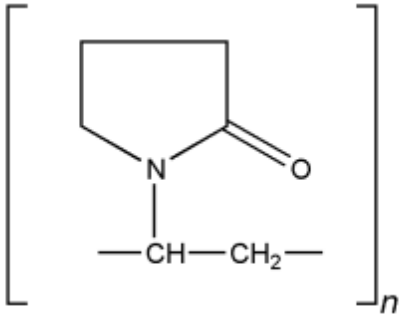

Fig 1.8 : Polyvinyl Pyrrolidone or Povidone(Rowe, Sheskey, Owen, 2005)

- Empirical Formula: (C6H9NO)n
- Molecular Weight: 2500–3000000

1.4.6.1 Functional Category

Disintegrant; dissolution aid; suspending agent; tablet binder.

1.4.6.2 Uses of povidone or PVP

- Carrier for drugs (10-25)
- Dispersing agents (upto 5)
- Eye drops (2-10)
- Suspending agent (upto 5)
- Tablet binder, tablet diluent, or coating agent (0.5-5)

1.4.6.3 Applications in Pharmaceutical Formulation or Technology

- Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid dosage forms. In tableting, povidone solutions are used as binders in wet granulation processes.
- Povidone is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol, or hydroalcoholic solutions.
- Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid dosage forms.

Povidone solutions may also be used as coating agents. Povidone is additionally used as a suspending, stabilizing, or viscosity increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.

(Rowe, Sheskey, Owen, 2005)

1.5: SHORT NOTES ON APIs USED IN THE EXPERIMENT

1.5.1. Amlodipine

Amlodipine is a long-acting 1,4-dihydropyridine calcium channel blocker. It acts primarily on vascular smooth muscle cells by stabilizing voltage-gated L-type calcium channels in their inactive conformation. By inhibiting the influx of calcium in smooth muscle cells, amlodipine prevents calcium-dependent myocyte contraction and vasoconstriction. A second proposed mechanism for the drug's vasodilatory effects involves pH-dependent inhibition of calcium influx via inhibition of smooth muscle carbonic anhydrase. Some studies have shown that amlodipine also exerts inhibitory effects on voltage-gated N-type calcium channels. N-type calcium channels located in the central nervous system may be involved in nociceptive signaling and pain sensation. Amlodipine is used to treat hypertension and chronic stable angina.

- Categories
  - ✓ Antihypertensive agents
  - ✓ Vasodilator agents
  - ✓ Calcium channel blockers
  - ✓ Antianginal agents

- Chemical Formula : $C_{20}H_{25}ClN_2O_5$

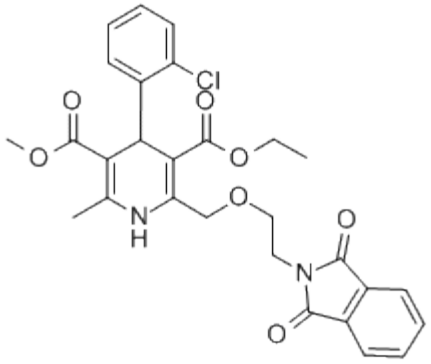

Fig 1.9: Amlodipine (DrugBank, 2015)

1.5.1.1Mechanism of action

Amlodipine decreases arterial smooth muscle contractility and subsequent vasoconstriction by inhibiting the influx of calcium ions through L-type calcium channels. Calcium ions entering the cell through these channels bind to calmodulin. Calcium-bound calmodulin then binds to and activates myosin light chain kinase (MLCK). Activated MLCK catalyzes the phosphorylation of the regulatory light chain subunit of myosin, a key step in muscle contraction. Signal amplification is achieved by calcium-induced calcium release from the sarcoplasmic reticulum through ryanodine receptors. Inhibition of the initial influx of calcium decreases the contractile activity of arterial smooth muscle cells and results in vasodilation. The vasodilatory effects of amlodipine result in an overall decrease in blood pressure. Amlodipine is a long-acting CCB that may be used to treat mild to moderate essential hypertension and exertion-related angina (chronic stable angina). Another possible mechanism is that amlodipine inhibits vascular smooth muscle carbonic anhydrase I activity causing cellular pH increases which may be involved in regulating intracelluar calcium influx through calcium channels.

1.5.1.2Indication

For the treatment of hypertension and chronic stable angina.

1.5.1.3 Pharmacodynamics

Amlodipine belongs to the dihydropyridine (DHP) class of calcium channel blockers (CCBs), the most widely used class of CCBs. There are at least five different types of calcium channels in Homo sapiens: L-, N-, P/Q-, R- and T-type. It was widely accepted that DHP CCBs target L-type calcium channels, the major channel in muscle cells that mediate contraction; however, some studies have indicated that amlodipine also binds to and inhibits N-type calcium channels (see references in Targets section). Similar to other DHP CCBs, amlodipine binds directly to inactive L-type calcium channels stabilizing their inactive conformation. Since arterial smooth muscle depolarizations are longer in duration than

cardiac muscle depolarizations, inactive channels are more prevalent in smooth muscle cells. Alternative splicing of the alpha-1 subunit of the channel gives amlodipine additional arterial selectivity. At therapeutic sub-toxic concentrations, amlodipine has little effect on cardiac myocytes and conduction cells.

1.5.1.4Pharmacokinetics

- Absorption: Amlodipine is slowly and almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations are reached 6-12 hour following oral administration. Its estimated bioavailability is 64-90%. Absorption is not affected by food.
- Protein binding: 97.5%
- Metabolism: Hepatic. Metabolized extensively (90%) to inactive metabolites via the cytochrome P450 3A4 isozyme.
- Route of elimination: Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.
- Half life: 30-50 hr
- Toxicity: Gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to an including shock with fatal outcome have been reported.

(DrugBank, 2015)

1.5.2 Propranolol

A widely used non-cardioselective beta-adrenergic antagonist. Propranolol is used in the treatment or prevention of many disorders including acute myocardial infarction, arrhythmias, angina pectoris, hypertension, hypertensive emergencies, hyperthyroidism, migraine, pheochromocytoma, menopause, and anxiety.

- Categories
  - ✓ Antiarrythmic agents
  - ✓ Antihypertensive agents
  - ✓ Vasodilator agents
  - ✓ Adrenergic beta blocker

- Chemical Formula: $C_{16}H_{21}NO_2$

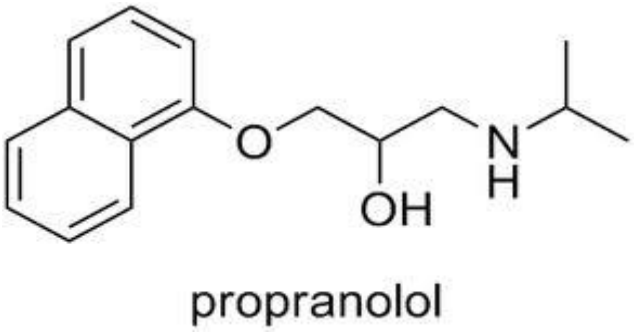

Fig 1.10 Propranolol (DrugBank, 2015)

1.5.2.1 Mechanism of action

Propranolol competes with sympathomimetic neurotransmitters such as catecholamines for binding at beta(1)-adrenergic receptors in the heart, inhibiting sympathetic stimulation. This results in a reduction in resting heart rate, cardiac output, systolic and diastolic blood pressure, and reflex orthostatic hypotension.

1.5.2.2 Indication

For the prophylaxis of migraine.

1.5.2.3 Pharmacodynamics

Propranolol, the prototype of the beta-adrenergic receptor antagonists, is a competitive, nonselective beta-blocker similar to nadolol without intrinsic sympathomimetic activity. Propanolol is a racemic compound; the l-isomer is responsible for adrenergic blocking activity.

1.5.2.4 Pharmacokinetics

- Absorption: Propranolol is almost completely absorbed from the GI tract; however, plasma concentrations attained are quite variable among individuals.
- Volume of distribution: 4L
- Protein binding: More than 90%
- Metabolism: Hepatic
- Route of elimination: Propranolol is extensively metabolized with most metabolites appearing in the urine.
- Half life: 4hours
- Toxicity: Symptoms of overdose include bradycardia, cardiac failure, hypotension, and brochospasm. LD_{50}=565 mg/kg (orally in mice).

(DrugBank, 2015)

Chapter Two

LITERATURE REVIEW

2.1 LITERATURE REVIEW

Flow property of individual Active Pharmaceutical Ingredients (API) and excipients both has an important role in drug manufacturing. If flow property of an excipient or an API is not good then it may affects many parameters of both tablets and capsules. Realizing the significance of flow property of excipients and APIs in mind, many scientists and researchers tried to study and finally determined the flow characteristics of different excipients and APIs. In last few decades lots of research works took place regarding different parameters of flow characteristics of different powder excipients and APIs.

In the earlier of the nineteenth century, at firth Gold and Palermo (Gold and Palermo, 1965)took an attempt to study the antistatic properties of tablet lubricants such as magnesium stearate, polyethylene glycol 4000, sodium lauryl sulfate and talc. The data indicated that those lubricants had the ability to lower the accumulation of static charges which results the flow of material through a tablet hopper. The study showed that different highly static materials influence the antistatic properties of those lubricants. If the concentration of lubricant was lower, the antistatic effectiveness was decreased.

In the last of the following year, Gold with other three researchers(Gold et al., 1966) compared the results obtained by the measurement of angle of repose of some commonly used glidants. Glidants had been chosen since they possessed subjective or indirect methods like angle of repose measurement. Those were fumed silicon dioxide, magnesium stearate, starch and talc in combination with other selected materials. Researchers observed that some widely used glidants might decrease the flow rate. The results they found that was the flow of glidants couldnot be reliably evaluated by measuring angle of repose. The research also demonstrated that angle of repose was not a reliable source for the evaluation of flow property of the concerned materials.

After 13 years in the year 1979, Bolhuis and his team (Bolhuis, Lerk, Moes, 1979) 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‡C 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.

After three years in the year 1982, a study was performed showing the effect of particle size on the compression mechanism and tensile strength of prepared tablets by two scientists, Mckenna and Mccafferty(Mckenna and Mccafferty, 1982). 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.

In the next year 1983, Chowhan and Yang(Chowhan and Yang, 1983) in their research paper determined the tensile strength of consolidated powder beds of spray-dried lactose and binary mixtures of lactose including different concentrations of glidants and/or lubricants. They measured the orifice flow rate of these powders by choosing an appropriate orifice diameter. They found that powder mixtures containing up to 1% glidant resulted in general in a decrease in the tensile strength and a raise in the flow rate as well as flow rate of powder mixtures containing simple glidants such as corn starch and microcrystalline cellulose at different concentrations was linearly related to the tensile strength.

Then subsequent to seven year later 1990, Tan and Newton (Newton and Tan, 1990)worked on 5 pharmaceutical excipients in the middle of 1990 and found that the flowability of size fractions of 5 pharmaceutical excipients was related to their capsule filling performance. They used angular, packing and shear tests, the samples were ranked in different relative orders of flowability. Flowability was reliant on the particle size, morphology and bulk density of the powder. They found that there was a major correlation between the values of coefficient of variation and the flow parameters of Carr’s compressibility, Hausner’s's ratio, angle of repose, Kawakita's equation constant and Jenike's flow factor. They also found that coefficient of variation was also related to the coefficient of variation of the powder bed bulk density and the variation in the compression stress.

Then after four years Kamath, Puri and Manbeck (Kamath et al., 1994)measured the flow properties such as cohesion and slope of the yield of wheat flour at various moisture contents by using the Jenike shear testing where time was not considered. Here the experiment was observed over a range of loading conditions. The observed value for cohesion study did not differ significantly but in case of slope, the value was significantly different. Besides, the flow properties of wheat flour at different moisture content and consolidation times of 12 hour and 24 hour did not differ significantly.

The same year, Schmidt and Rubensdorfer (Schmidt and Rubensdorfer, 1994)in their research paper evaluated and compared powder characteristics and tableting properties of Ludipress, a lactose-based, free flowing granule containing povidone and crospovidon. They evaluated flowability, bulk density, tapped density, Hausner’s ratio, angle of repose and particle size distribution of Ludipress. They examined the particle morphology by using scanning electron microscopy (SEM). They found that Ludipress samples revealed a good batch-to-batch uniformity and flow characteristics compared to the physical blend and other excipients investigated.

The next year, in middle of 1995, Amidon and Houghton (Amidon and Houghton,1995)worked on the effects of moisture on the mechanical and powder flow

properties of microcrystalline cellulose and finally they found powder flow was shown to decrease with increasing moisture content.

The effect of eleven pharmaceutical excipients with Avicel PHI02 SCG was investigated by two scientists, Flemming and Mielck (Flemming and Mielck, 1995)in the same year. Physical characteristics like particle size distribution, true and bulk densities and flow rates had been evaluated. The study yields, for micro-tableting purpose flow rates were calculated on modern high speed rotary tableting machine, and also from very narrow orifices.

A comparative investigation had been performed in the next year by Talukdar and other scientists (Talukdar et al.,1996)between xanthan gum and HPMC which act as hydrophilic matrix-forming agents. They observed the compaction characteristics and drug release behavior of these materials. Though the compaction characteristics were found similar but the flow characteristics were different. HPMC is less flowable than xanthan gum which significantly affects the drug release profiles of these potential excipients.

Then in the year 1998, Feeley and his co-workers (Feeley et al.,1998)characterized the surface thermodynamic properties of two supposedly equivalent batches of salbutamol sulphate in order to focusing on the surface energetic changes induced on micronisation by Inverse gas chromatography (IGC). A powder flow analyser was used to check out the relationship between powder flow and the surface energetic properties. The potential of these techniques to identify and measure differences in powder samples, before and after micronisation was found. The result also indicated that surface energy differences detected by IGC might be related to important secondary processing properties such as powder flow.

In the twentieth century, Taylor (Taylor et al., 2000) and his coworkers tested the flow properties of typical tablet and capsule formulation excipients, active ingredients and the representative formulation with recent and novel measurement of flow techniques for identifying a definite and precise testing operation for powder flow measurement. It is compared with the screening method of earlier tablet and capsule formulation. Here the test parameters were angle of repose, compressibility index and critical orifice. After establishment of the empirical composite index, powder flow had been determined with respect to principal component, analysis of angle of repose and critical orifice of the powder material. The data that was found from the research showed the first principal component accounted for 72.8% of data variability with the obtained scores associated with this principal component score can serve as an index of flowability. On the other hand, the data found from vibrating spatula and avalanching methods were not reproducible. Lastly, the research proved that improvements of test instruments andfurther studies are necessary for better assessment of those approaches.

In the same year Jivraj, Martini and Thomson (Jivraj et al., 2000) observed the effect of various excipients which had been used as fillers in direct compression formulations. The tablet dosage form was considered as it account for more than 80% of the administered

dosage form. Here the study had given emphasis on the expected result in accordance with their functionality. They wanted to find out the reason to give emphasis on choosing excipients depending on their function. But the study did not give enough effective finding rather stands as a narrative description.

Again in later 2000, two researchers Podczeck and Newton (Newton and Podczeck , 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.

Another research was conducted in the next year 2001, Hancock (Hancock et al., 2001)and his research fellow evaluated two recently developed matrix forming polymers like cross-linked high-amylose starch and polyacrylic acid. The operating parameters were powder flow and compact mechanical properties. The scientists also compared the properties with two previously established matrix-forming polymers such as hydroxypropyl methylcellulose and hydroxypropyl cellulose. The research showed that, the four materials were different in particle morphology, size distribution and true density. The materials also exhibited different powder flow, compact ductility, compact elasticity and compact tensile strength. The research concluded that, these excipients can be recommended for formulating solid dosage forms after considering their physical properties and performance.

The same year Gabaude (Gabaude et al., 2001) and his fellow researchers compared between four techniques. For the measurement of powder flow properties, two methods werere considered that were packing and rearrangement under pressure methods or shear cell measurement methods. The reduction of the powder bed volume under low pressures wass evaluated by two compressibility methods such as uniaxial press and volumenometer. Flow functions were determined from shear cell measurements using a Johanson Indicizer Tester. The packing coefficient obtained from reduction of the powder bed volume appears to be a reliable estimate of powder flow properties. The properties such as cohesive or free flowing was actually well interconnected with shear cell measurements and it was more precise than classical flowability tests recommended by the European Pharmacopoeia. The research concluded with the statement that this method was easy to use with a quite accurate estimation of powder flow properties of new drug substances and consumed a small amount of powders less than 1g.

In the March of 2002, an Indian scientist, Vijay Kumar (Kumar, Reus-Medina, Yang, 2002) along with two others conducted a study with UICEL that was actually a new cellulose-based tabletting excipient. This had 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.

In the midth of the march 2003, Mullarney (Mullarney et al., 2003) and his research fellow worked on the physical, flow, and mechanical properties of four common pharmaceutical sweeteners, such as Sucrose, acesulfame potassium (Sunett®), saccharin sodium, and aspartame to assess their relative manufacturability in solid dosage formulations. They measured powder flow and cohesivity as well as compact mechanical properties such as ductility, elasticity, and tensile strength. They found sucrose and acesulfame potassium demonstrated excellent flowability. Saccharin sodium and aspartame demonstrated poor flowability and superior compact strength relative to sucrose and acesulfame, despite their noticeably higher brittleness.

In the end of that year, Zhang (Zhang, Law, Chakrabarti, 2003) and his research fellow investigated the basic physico-chemical property and binding functionality of commonly used commercial direct compression binders in 2003. They analyzed the compressibility of microcrystalline cellulose (MCC), starch, lactose, dicalcium phosphate (DCP), and sugar using compression parameters derived from the Heckel, Kawakita, and Cooper-Eaton equations. They demonstrated that MCC had moderate flowability, excellent compressibility, and extremely good compact hardness; with some exceptions, starch, lactose, and sugar generally demonstrated moderate flowability, compressibility, and hardness on the other hand dicalcium phosphate had outstanding flowability, but poor compressibility and hardness.

In the next year 2004, Bhattachar (Bhattachar et al., 2004) and his research fellows studied on the flow properties of pharmaceutical powders and blends used in solid oral dosage forms which were important consideration during dosage form development. They adapted vibratory feeder method which was a flow measurement technique that quantifies avalanche flow that used for measurement of the flow properties of common pharmaceutical powders used in solid oral dosage forms. They measured 17 different powders with the instrument and results are described as a powder flow index (PFI). They found the PFI tendency of the powders show a relationship with flow properties. They also measured the flow property with

a commercially available avalanche instrument, the Aero-Flow™, and the results were detailed as the mean time to avalanche (MTA) in view of the fact that the two instruments analyze the avalanche by different algorithms, the results were compared with nonparametric statistical evaluation of ranked data. Finally they recommended a procedure for measurement of powder flow with the vibratory feeder.

In the same year, Lindberg (Lindberg et al., 2004) and his research team evaluated flow properties of four different tablet formulation having poor flowability for direct compression using five different techniques. The tableting parameters were Hausner ratio, powder rheometer and other flow behavior. The behavior of three of the formulation out of four was observed. The result was compared with the value of the flowability measurements. The correlated rank order of the formulations was considered the same with all the techniques. The measured flow properties directly reflect the behavior of the tablet formulation during powder mixture procedure.

Again in 2004, The same year Sinka, Schneider and Cocks (Sinka et al., 2004) investigated the flow behaviour of four pharmaceutical powders using a model known as shoe-die-filling system. The variation of mass delivered to the die referred to the measurement of flowability. Considering the context of pharmaceutical powders, the concept of critical velocity regarding incomplete filling was observed. The filling process was recorded using a high-speed video system. It may allow observing the different flow patterns and influences of the critical velocity. The influence of humidity for one of the powders was found to be negligible. In fact the process such as die opening and die filling and condition of operation such as in air or vacuum significantly change the flow behavior.

In the similar year, Thalberg (Thalberg, Lindholm, Axelsson, 2004) and his research fellows in their research paper characterized a series of placebo powders for inhalation concerning bulk density and powder flowability using different techniques. They found a modified Hausner's Ratio was obtained by measurement of the poured and the compressed bulk densities as well as they investigated angle of repose, the avalanching behaviour using the AeroFlow, and the yield strength using the Uniaxial tester. They found a good correlation between the modified Hausner's Ratio and the angle of repose and AeroFlow was suitable for powders with a low percentage of fine particles, but could not discriminate between the more cohesive powders. They determined that the addition of micronized particles has a strong manipulate on the flowability of ordered mixtures, while in-between sized particles have little impact on the powder flow.

Again in the same year 2004, Jonat (Jonat et al., 2004) along with his research group studied the glidant properties of compacted hydrophilic and hydrophobic colloidal silicon dioxides and compared with respect to mixing time and mixer type using microcrystalline cellulose, pregelatinized starch and α-lactose-monohydrate as model excipients. They also performed flowability studies, including angle of repose measurements and a novel dynamic conveyor belt method and found differences in the flow enhancement between the colloidal silicon

dioxide types. They found that an influence of mixing conditions on flowability was hydrophilic colloidal silicon dioxide. They identified the influence of size and distribution of the colloidal silicon dioxide particles on the surface of the excipient, mixing time, mixer type. In addition, they found after moisture studies that colloidal silicon dioxide protects the excipients against a flowability decrease caused by humidity.

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. 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. (Fitzpatrick et al.,2004)

In the following year 2005, Kim (Kim, Chen, Pearce, 2005) and his research fellows studied 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 flowability. They found that skim milk powder flows well compared to the other powders because the surface was 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 identified 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 influenced the flowability of powders, the flowability of powders was powerfully influenced by the surface composition of powders, chiefly for fat-containing powders.

In the same year 2005, Kachrimanis (Kachrimanis, Petrides, Malamataris, 2005) along with his research fellows studied effects of cylindrical orifice length and diameter on the flow rate of three commonly used pharmaceutical direct compression diluents lactose, dibasic calcium phosphate dihydrate and pregelatinised starch. They also evaluated the powder particle characteristics e.g., particle size, aspect ratio, roundness and convexity) and the packing properties e.g.,true, bulk and tapped density. They determined the flow rate was for three different sieve fractions through a series of tiny tableting dies of different orifice diameter and thickness. They found that flow rate decreased with the increase of the orifice length for the small diameter but for the large diameter was increased with the orifice length. Finally they stated that orifice length is the third most influential variable after the orifice diameter and particle size, followed by the bulk density, the difference between bulk and tapped densities and the particle convexity.

Then two year later, in the year 2007, Jacob (Jacob et al., 2007) and his research fellows conducted a study on flow property of co-processed particles of microcrystalline cellulose (MCC) and mannitol. They fabricated both the excipients by spray drying process to be used as a direct compression excipient in fast dissolving tablet formulation. They examined composite particles for their powder and compression properties. They observed that that an increase in the MCC proportion imparted greater compressibility to the composite particles, but the flowability of these mixtures was decreased. MCC and mannitol had been widely used in the formulation of fast dissolving tablets. They found the non-wetting property of the hard compact central core may delay the disintegration time. They optimized the ratio of mannitol and MCC and found had optimized powder and compressibility characteristics with fast disintegrating property. They concluded that higher rate of powder flow could indirectly influence the rate of disintegration.

In earlier of the same year, Faqih (Faqih et al., 2007) and his research fellows studied on flow in a rotating drum and flow in bench scale hoppers. They studied flow characteristics 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.

Then next year, Shah (Shah, Tawakkul, Khan, 2008) and his team evaluated the flow of pharmaceutical powders and granules using compendial and non-compendial methods. They evaluated Angle of repose, bulk density, tapped density, Carr's compressibility index, and Hausner's ratios. They also determined cohesivity index, caking strength, and flow stability of samples which includes different grades of magnesium stearate powder including bovine, vegetable, and food grade, physical mixture powder blend consisting of a model formulation, granules prepared by various methods including slugging, high shear granulator, and fluid bed dryer. They observed that the compendial methods were often non-discriminating for minor variations in powder flow. They stated that cohesivity, and caking strength was helpful in understanding the flow characteristics of pharmaceutical systems.

In the same year 2008, Feeley (Feeley et al., 2008) and his research fellows employed Inverse gas chromatography (IGC) to characterise the surface thermodynamic properties of two nominally equivalent batches of salbutamol sulphate. They highlighted on surface energetic changes induced on micronisation. They used powder flow avalanching analyser which explored the relationship between powder flow and the surface energetic properties. They found a result which demonstrated the potential of these techniques to detect and quantify differences in powder samples, before and after micronisation. They also indicated that the

surface energy differences detected by Inverse gas chromatography (IGC) could be linked to important secondary processing properties such as powder flow.

Again in the same year 2008, Hou and Sun (Hou and Sun, 2008) investigated the effects of particle size, morphology, particle density, and surface silicification, on powder flow properties using a ring shear tester. They took 11 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, and studied them. They found that smaller particles always led to poorer powder flow properties. They identified that mechanism of the detrimental effect of particle size reduction on flow properties and that was the larger powder specific surface area. They found that flow properties of Celphere were considerably better than Avicel of comparable particles size and 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.

In early of the next year 2009, Emery (Emery et al., 2009) and his co research workers worked on the effect of moisture content on four pharmaceutical powders, an active pharmaceutical ingredient (API), Aspartame, Hydroxypropyl Methylcellulose (HPMC), and Respitose. They found the API and Respitose powders were nonhygroscopic. They measured the flow property using the Jenike shear index, the Hausner's Ratio, the Carr Index, and the static and dynamic angles of repose. Finally they found that flowability of Aspartame improved with an increase in moisture content, which was credited to the formation of large, round agglomerates as well as the flowability of HPMC decreased with a raised in moisture content, recognized to the increasing strength of liquid bridges.

Then one year later, in early 2010, Seppala (Seppala et al., 2010) and his research team developed a new method to get a reliable powder flow characteristics using only 1 to 2 g of powder. In pharmaceutical industry, it was frequently significant to directly measure real powder flow rate from a small amount of powder. It was necessary to determine powder flow properties of new active pharmaceutical ingredient (API) in an early stage of the development when the amount of API was limited. They introduced a new direct method to measure powder flow when the material is poorly flowing and the amount of material was small. Their system was very simple and consisted of a flow chamber and electronic balance and an automated optical detection system. They stated that for each measurement only 1 to 2 g of sample was required. They selected sugar excipients, three grades of microcrystalline cellulose, and APIs e.g., caffeine, carbamazepine, and paracetamol. They also classified freely flowing, intermediate flowing, and poorly flowing powders, respectively. This classification was based on their results. Their method provided a new tool for a rapid determination of flowing characteristics of powders (e.g., inhalation powders) and granules at a small scale.

In the same year 2010, the one and only scientist Sun(Sun, 2010) discovered that in tablet manufacturing process an inadequate powder flow led to a great problem. Besides, a minimum knowledge of flow properties for efficient pharmaceutical tablet development was required for successful tableting result. The finding was achieved in order to discovered a powder exhibiting minimum acceptable flow properties on a high speed tablet press. The experiment showed that microcrystalline cellulose lies in the borderline between acceptable and poor powder flow area during the tableting process. The data also could serve as a reference value for comparing with other prototype formulation. The research concluded that a poor flowing powder exhibit flow problems should be avoided and further implementation of this approach can minimize the problem associated with flow measurement during large scale production.

Again in the same year Yu (Yu et al., 2010) and his research fellows established a modeling approach that can be used to predict bulk powder flowability of pharmaceutical materials from their particle size and shape distributions. They characterized the particle size and shape distributions of 23 commonly used pharmaceutical excipients and 38 binary blends. They analyzed the flow properties using Schulze Ring Shear Tester at a fixed humidity condition and used partial least squares (PLS) approach to construct the mathematical model. Finally they found that particle size and shape play an important role in determining the powder flow behavior.

Over again in the year 2010, Sarraguca (Sarraguca et al., 2010) and his co-research fellows studied the flow properties of pharmaceutical excipientss using near infrared spectroscopy. They demonstrated that physical properties of pharmaceutical powders are of topmost significance in the pharmaceutical industry. They observed the critical major properties of flowability using processes like blending, tablet compression, capsule filling and transportation using angle of repose, Carr's index and Hausner's ratio. They used near infrared spectroscopy because it was fast and low-cost analytical technique to determine the parameters of flow properties of pharmaceutical powders based on active ingredient paracetamol. They recorded the spectra on a Fourier-transform near infrared spectrometer in which the parameters were the angle of repose, true and tapped density. They made a comparison between near infrared based properties and reference methods results. They found that the physical properties affect the flowability of pharmaceutical powders.

In the following year Chattoraj, Shi and Sun (Chattoraj et al., 2011) demonstrated that poor flow properties hindered the easy handling of powders during industrial-scale processing. In their experiment, they showed that powder flow could be considerably improved by reducing the cohesion of powders by coating them with nanosized guest particles. They analytically investigated the effects of the flow behavior of a highly cohesive and poorly flowing grade of microcrystalline cellulose powder (Avicel PH105). Optimum flow enhancement had been made with specified preparation at vigorous mixtures. The flow properties of nanocoated Avicel PH105 were comparable to those of Avicel PH102, which exhibited adequate flowability for processing on a high-speed tablet press. The result showed that the technique proved as a potential source for addressing industrial powder handling problems caused by poor powder flow properties.

Most recently Vanarase, Osorio, and Muzzio (Vanarase et al., 2013) focused on two aspects of continuous powder mixing such as characterizing the effects of material properties on the bulk powder flow behavior, and developing continuous blending strategies suitable for cohesive materials. The relative effects of process parameters and material properties on the bulk powder flow behavior were analyzed by a PLS analysis of the output parameters. It included mean residence time, and axial dispersion coefficient. The function of input parameters was impeller speed, flow rate, bulk density and cohesion. The study showed that means residence time was mainly affected by the bulk density and impeller speed. On the other hand, the axial dispersion coefficient was affected by impeller speed and cohesion. The research also demonstrated that a combination of high shear and low shear mixing with high-shear mixing as a first step exhibited an optimal mixing strategy for blending cohesive materials.

Again in 2013 another 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 & 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.	Starch	MERK, Germany
2.	Polyethylene glycol	MERK, Germany
3.	Carboxymethyl cellulose	MERK, Germany
4.	Zinc stearate	MERK, Germany
5.	Talc	MERK, Germany

3.1.3 Equipments and Instruments:

Table 3.2: List of instruments through this research work

SL no	Equipments name	Source (Supplier name)	Origin
1.	Electronic 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: 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

SL no	Apparatus name
1.	Beaker
2.	Test tubes
3.	Aluminium foil paper
4.	Cling wrap
5.	Morter & pastles
6.	Spatula
7.	Measuring cylinder
8.	Funnel
9.	Conical flask
10.	White paper
11.	Scale
12.	Glass rod & stand

3.2 METHODS

3.2.1Preparation of mixture of formula

Several formulas of a combination of excipients which includes diluents, lubricants, disintegrants, binders were made except antiadherent. Various formulas were made of 15 g based on the required quantity to test which are denoted by F1, F2, F3 and so on.The particular amount of the formula was taken.After preparing 15g of formula (F1,F2,F3,F4) specific antiadherent was mixed with it in different fixed and justified ratio. For this formula, zinc stearate was used. The required amount of both zinc stearate and F1, F2, F3 and F4 was calculated for preparing each 3g of mixture in five different ratio.

All the ingredients were weighed in a electronic balance,settled in a five testtubes and mixed well.The test tubes were labelled properly.Those testtubes were then ready for measuring individual flow properties by observing its bulk volume, tapped volume, which ultimately yielded carr's index, hausner ratio, and angle of repose as well. The process was continued to evaluate the difference in flow properties while adding different ratio of zinc stearate. In my research I also used 0.0625 gm of two API (Amlodopine and Propranolol) to see the difference in flow characteristics of APIs and excipients.

3.2.2 Flow property measurement:

3.2.2.1 Determination of bulk volume:

- At first the mixture of materials in a test tube was transferred to a dry measuring cylinder.
- The volume was measured after manually tapping the cylinder two times on a flat table top surface.
- The achieved volume is the bulk volume which was documented.

3.2.2.2 Determination of tapped volume:

- After measuring the bulk volume, the mixture of materials in the measuring cylinder was tapped manually 50 times and above until little further volume change is observed.
- The tapping is achieved by raising the cylinder and allowing it to drop under a specified distance.
- The measured volume was documented.

3.2.2.3 Calculation of Carr's index and Hausner ratio:

The compressibility index and Hausner ratio were calculated by the given formula

$$Compressibility\ Index = 100 \times \left(\frac{V_o - V_f}{V_o} \right)$$

$$Hausner\ Ratio = \frac{V_o}{V_f}$$

Where,
Vo = Bulk volume
Vf = Tapped volume

3.2.2.4 Measurement of Angle of repose:

In this research project fixed funnel method was used among the three certified methods

3.2.2.4.1 Procedure:

- First of all, funnel made of plastic, glass or stainless steel was set with the holding stand tightly.
- The funnel was fixed in a place, 4 cm above the bench surface.
- On the bench surface, a piece of paper was placed.
- The mixture of the running test tube was poured through the funnel without incorporating external pressure or stress.
- The powder mixture formed a cone on the paper.
- After the cone from 5g of sample was built, height of the granules forming the cone (h) in cm and the radius (r) of the base in cm were measured.
- The angle of repose was calculated by the given formula and documented.

$$\theta_r = \tan^{-1}\left(\frac{height(h)}{width(w)} \right)$$

Where, h = height of the powder cone from the base; r = radius of the conical pile.

3.2.3 Preparation of Formulas

3.2.3.1 Preparation of Formula 1 (F1):

By choosing different excipients from different classes except antiadherents, formula 1 (F1) was prepared. Here the selected excipients from a particular class will serve the properties of itself in that range of amount not the others.

3.4 Table: The following amounts of excipients (given with their use) were taken for the preparation of Formula 1 (F1)-15g

Ingredients name	Purpose of use	Percentage quantity	Amount in 10 gm
Starch	Diluent	40%	6g
PEG	Binder	25%	3.75g
CMC	Disintegrant	20%	3g
Talc	Lubricant	15%	2.25g
		Total= 100%	Total= 15g

After preparing 15g of F1, specific antiadherent was mixed with it in different fixed and justified ratio. For this formula, zinc stearate was used. The required amount of both zinc stearate and F1 was calculated for preparing each 3g of mixture in five different ratio.

3.5 Table: The amount of zinc stearate and F1 in different ratio in 3g

Ratio	Zinc stearate : F1	Amount of zinc stearate : F1 (in gm)
1	5% : 95%	0.15 : 2.85
2	6% : 94%	0.18 : 2.82
3	7% : 93%	0.21:2.79
4	8% : 92%	0.24:2.76
5	9% :91%	0.27:2.73

3.2.3.2 Preparation of Formula 2 (F2):

By choosing different excipients from different classes except antiadherents, formula 2 (F2) was prepared. Here the selected excipients from a particular class will serve the properties of itself in that range of amount not the others

3.6 Table: The following amounts of excipients (given with their use) were taken for the preparation of Formula 2 (F2)-15g

Ingredients name	Purpose of use	Percentage quantity	Amount in 10 gm
Starch	Diluent	40%	6g
PEG	Binder	25%	3.75g
CMC	Disintegrant	20%	3g
Talc	Lubricant	15%	2.25g
		Total= 100%	Total= 15g

After preparing 15g of F2, specific antiadherent was mixed with it in different fixed and justified ratio. For this formula, zinc stearate was used. The required amount of both zinc stearate and F2was calculated for preparing each 3g of mixture in five different ratio.

3.7 Table: The amount of zinc stearate and F2 in different ratio in 3g

Ratio	Zinc stearate : F2	Amount of zinc stearate : F2 (in gm)
1	8% :92%	0.24 : 2.78
2	10% :90%	0.3 : 2.71
3	12% :88%	0.36 : 2.64
4	14% :86%	0.42 : 2.58
5	16% :84%	0.48 : 2.52

3.2.3.3 Preparation of Formula 3 (F3):

By choosing different excipients from different classes except antiadherents, formula 3 (F3) was prepared. Here the selected excipients from a particular class will serve the properties of itself in that range of amount not the others.

3.8 Table: The following amounts of excipients (given with their use) were taken for the preparation of Formula 3 (3)-15g

Ingredients name	Purpose of use	Percentage quantity	Amount in 10 gm
Starch	Diluent	40%	6g
PEG	Binder	25%	3.75g
CMC	Disintegrant	20%	3g
Talc	Lubricant	15%	2.25g
		Total= 100%	Total= 15g

After preparing 15g of F3, specific antiadherent was mixed with it in different fixed and justified ratio. For this formula, zinc stearate was used. The required amount of both zinc stearate and F3 was calculated for preparing each 3g of mixture in five different ratio.

3.9 Table: The amount of zinc stearate and F3 in different ratio in 3g

Ratio	Zinc stearate : F3	Amount of zinc stearate :F3(in gm)
1	10% :90%	0.3 : 2.71
2	12% :88%	0.36 : 2.64
3	14% :86%	0.42 : 2.58
4	16% :84%	0.48 : 2.52
5	18% : 82%	0.54 : 2.46

3.2.3.4 Preparation of Formula 4 (F4):

By choosing different excipients from different classes except antiadherents, formula 4 (F4) was prepared. Here the selected excipients from a particular class will serve the properties of itself in that range of amount not the others.

3.10 Table: The following amounts of excipients (given with their use) were taken for the preparation of Formula 4 (F4)-15g

Ingredients name	Purpose of use	Percentage quantity	Amount in 10 gm
Starch	Diluent	40%	6g
PEG	Binder	25%	3.75g
CMC	Disintegrant	20%	3g
Talc	Lubricant	15%	2.25g
		Total= 100%	Total= 15g

After preparing 15g of F4, specific antiadherent was mixed with it in different fixed and justified ratio. For this formula, zinc stearate was used. The required amount of both zinc stearate and F4 was calculated for preparing each 3g of mixture in five different ratio.

3.11Table: The amount of zinc stearate and F4 in different ratio in 3g

Ratio	Zinc stearate : F4	Amount of zinc stearate :F3(in gm)
1	14% :86%	0.42 : 2.58
2	15% :85%	0.45 : 2.55
3	16% :84%	0.48 : 2.52
4	17% : 83%	0.51 : 2.49
5	18% : 82%	0.54 : 2.46

Chapter Four

RESULTS

4.1 RESULTS

4.1.1 Calculation of flow properties of excipients and API

4.1.1.1 Calculation of excipients and APIs for Formula 1

The flow property of excipients and APIs were measured by calculating their Carr's index, Hausner ratio and angle of repose. For calculating Carr's index and Hausner ratio, their individual bulk volume and tapped volume were measured five times and the average value was taken. The observed value is given below:

4.1 Table: Values of Carr's Index and Hausner Ratio of excipients for Formula 1

Ratio	Bulk volume, V_o (ml)	Most acceptable bulk volume, V_o (ml)	Tapped volume, V_f (ml)	Most acceptable tapped volume, V_f (ml)	Hausner ratio (V_o/V_f)	Carr's index $100x\{(V_o-V_f)/V_f\}$
Ratio 1	9 10 9.1 10 9	10	7.5 7.6 7.8 7.5 7.5	7.5	1.33	33.33
Ratio 2	9.1 9.2 9.5 9.5 9.5	9.5	7.4 7.4 7.3 7.3 7.6	7.3	1.30	30.14
Ratio 3	9.1 9.2 9.5 9.5 9.5	9.5	7.4 7.4 7.3 7.3 7.6	7.3	1.30	30.14
Ratio 4	9.8 9.6 9.6 9.8 9.8	9.8	7.7 8 8.1 8 7.7	7.7	1.27	27.27
Ratio 5	8.1 8.3 8.3 8.6 9	9	7.2 7.1 7.4 7.3 7.2	7.1	1.27	26.76

4.2 Table: Values of Carr's Index and Hausner Ratio of excipients with API (Amlodipine) for Formula 1

Ratio	Bulk volume, V_o (ml)	Most acceptable bulk volume, V_o (ml)	Tapped volume, V_f (ml)	Most acceptable tapped volume, V_f (ml)	Hausner ratio (V_o/V_f)	Carr's index $100x\{(V_o-V_f)/V_f\}$
Ratio 1	4.1 3.9 3.9 3.7 3.7	4.1	3.1 3.2 3.2 3.1 3.1	3.1	1.32	32.26
Ratio 2	4.2 3.9 4 4.2 3.9	4.2	3.3 3.3 3.4 3.3 3.4	3.3	1.27	27.27
Ratio 3	4.1 4.1 4.2 4.2 4.1	4.2	3.4 3.3 3.3 3.3 3.3	3.3	1.27	27.27
Ratio 4	3.9 4 4 4 3.9	4	3.3 3.3 3.2 3.2 3.3	3.2	1.25	25.81
Ratio 5	3.9 3.8 3.7 3.7 3.8	3.9	3.2 3.2 3.3 3.2 3.2	3.2	1.22	21.88

4.3 Table: Values of Carr's Index and Hausner Ratio of excipients with API (Propranolol) for Formula 1

Ratio	Bulk volume, V_o (ml)	Most acceptable bulk volume, V_o (ml)	Tapped volume, V_f (ml)	Most acceptable tapped volume, V_f (ml)	Hausner ratio (V_o/V_f)	Carr's index $100x\{(V_o-V_f)/V_f\}$
Ratio 1	4.1 4.1 4 4 4.1	4.1	3.1 3.3 3.1 3.2 3.3	3.1	1.32	32.26
Ratio 2	3.9 4 4 3.9 3.8	4	3.3 3.3 3.1 3.3 3.1	3.1	1.29	29.03
Ratio 3	3.9 4 4 3.9 3.8	4	3.3 3.3 3.1 3.3 3.1	3.1	1.29	29.03
Ratio 4	4.1 4.1 4.2 4.2 4.1	4.2	3.4 3.3 3.3 3.3 3.3	3..3	1.27	27.27
Ratio 5	3.9 4 4 4 3.9	4	3.2 3.2 3.3 3.2 3.2	3.2	1.25	25.8

By plotting percentage ratio of zinc stearate in X-axis and respected Carr's index in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, Carr's index of any set of excipients and APIs can be achieved.

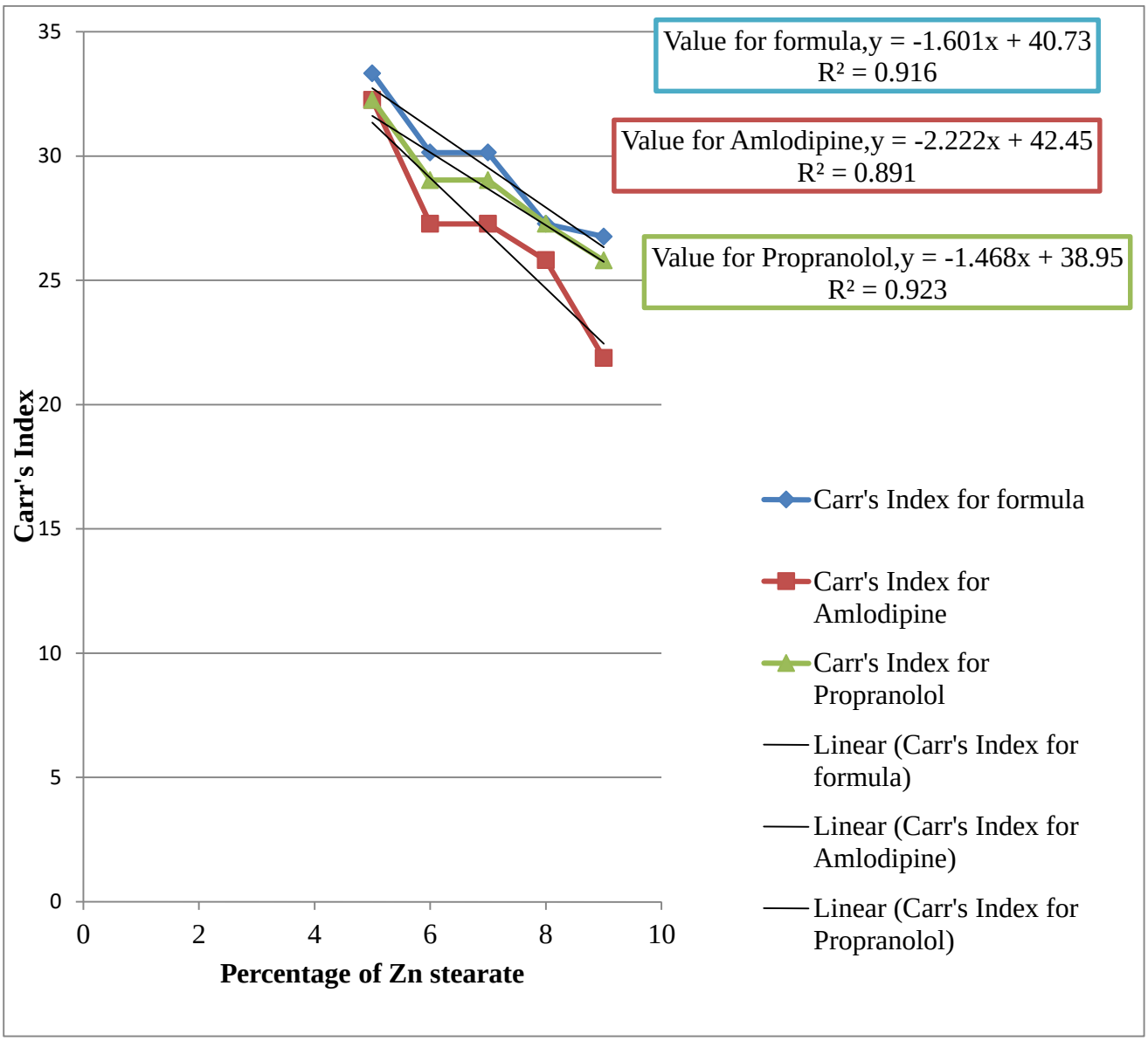

Figure 4.1: A percentage ratio of zinc stearate versus Carr's index graph

By plotting percentage ratio of zinc stearate in X-axis and respected Hausner ratio in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, Hausner ratio of any set of excipients and APIs can be achieved.

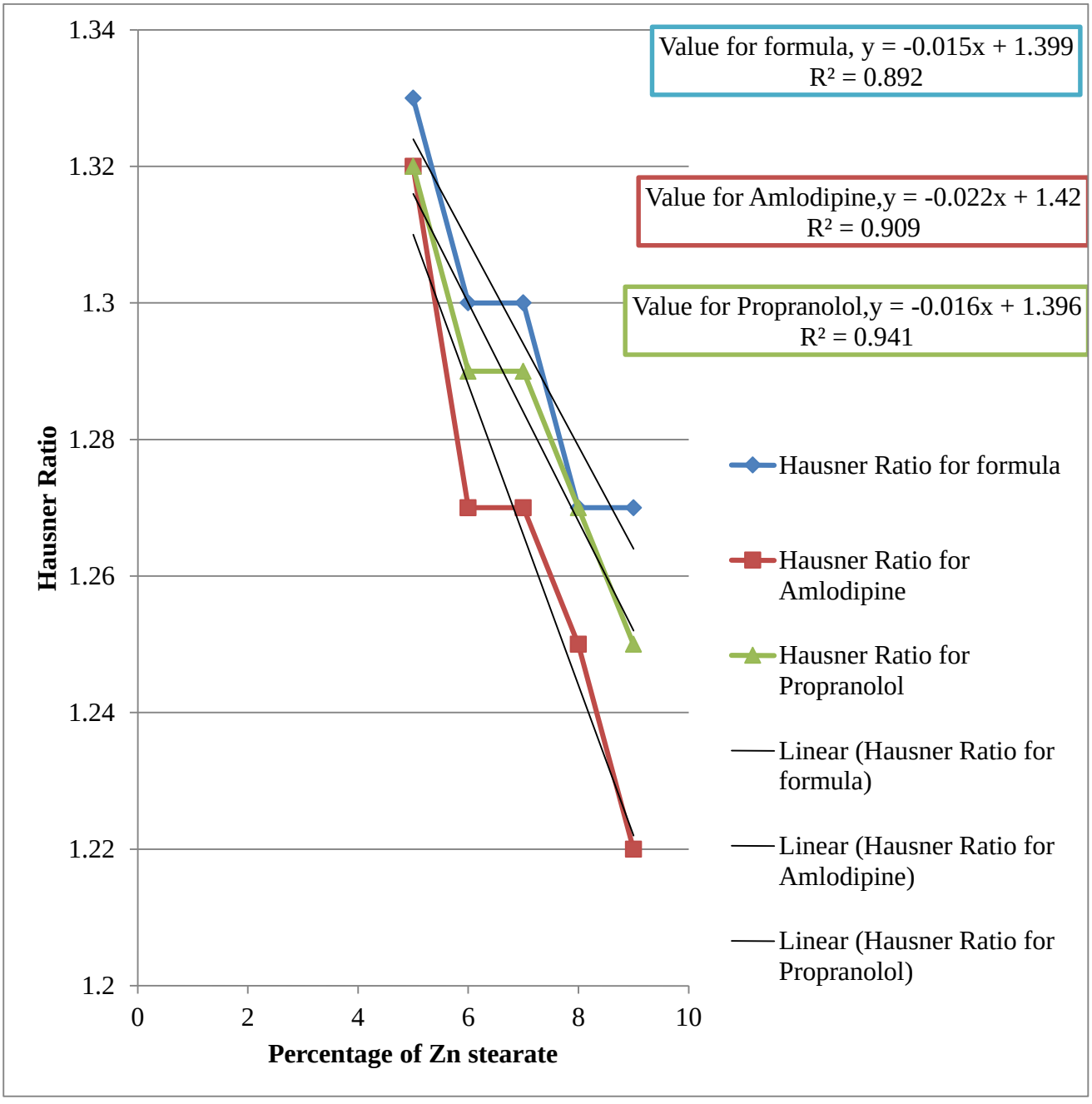

Figure 4.2: A percentage ratio of zinc stearate versus Hausner ratio graph

The angle of repose of Formula 1 was calculated by their cone height and radius which were measured five times and the average value was taken. The observed value is given below:

4.4 Table: Value of Angle of Repose of excipients for Formula 1

Ratio	Height of the pile, h (cm)	Diameter of the pile, 2r (cm)	Radius of the pile, r (cm)	Angle of repose $\tan^{-1} h/r$	Average value of angle of repose
Ratio 1	1.6 1.6 1.6 1.6 1.6	3.86 3.82 3.98 3.9 3.86	1.93 1.91 1.99 1.95 1.93	39.65 39.95 38.57 39.37 39.65	39.44
Ratio 2	1.6 1.6 1.6 1.6 1.6	3.86 3.9 3.82 3.98 4.08	1.93 1.95 1.91 1.99 2.04	39.65 39.37 39.95 38.57 38.11	39.13
Ratio 3	1.6 1.62 1.6 1.61 1.6	4.08 4.04 4.06 4.08 3.98	2.04 2.02 2.03 2.04 1.99	38.11 38.38 38.24 38.28 38.57	38.31
Ratio 4	1.58 1.59 1.58 1.58 1.59	4.06 4.1 4.16 4.18 4.08	2.03 2.05 2.08 2.09 2.04	37.89 37.79 37.22 37.08 37.93	37.58
Ratio 5	1.5 1.45 1.5 1.51 1.5	4.07 3.98 4.02 4.04 4.08	2.035 1.99 2.01 2.02 2.04	36.39 36.079 36.73 36.78 36.33	36.46

4.5Table: Value of Angle of Repose of excipients with API (Amlodipine) for Formula 1

Ratio	Height of the pile, h (cm)	Diameter of the pile, 2r (cm)	Radius of the pile, r (cm)	Angle of repose $\tan^{-1} h/r$	Average value of Angle of Repose
Ratio 1	1.2	2.8	1.4	40.60	
	1.23	3	1.5	39.35	
	1.21	3	1.5	38.89	39.27
	1.21	3.04	1.52	38.52	
	1.23	3.04	1.52	38.98	
Ratio 2	1.21	3.04	1.52	38.52	
	1.23	3.04	1.52	38.98	
	1.23	3.06	1.53	38.79	38.77
	1.24	3.06	1.53	39.02	
	1.21	3.04	1.52	38.52	
Ratio 3	1.23	3.2	1.6	37.55	
	1.22	3.2	1.6	37.33	
	1.22	3.1	1.55	38.21	37.55
	1.22	3.2	1.6	37.33	
	1.22	3.2	1.6	37.33	
Ratio 4	1.24	3.22	1.61	37.60	
	1.24	3.24	1.62	37.43	
	1.23	3.24	1.62	37.21	37.19
	1.23	3.3	1.65	36.87	
	1.23	3.28	1.64	36.86	
Ratio 5	1.23	3.3	1.65	36.87	
	1.24	3.32	1.66	36.73	
	1.23	3.32	1.66	36.54	36.76
	1.24	3.3	1.65	36.92	
	1.23	3.32	1.66	36.73	

4.6Table: Value of Angle of Repose of excipients with API (Propranolol) for Formula 1

Ratio	Height of the pile, h (cm)	Diameter of the pile, 2r (cm)	Radius of the pile, r (cm)	Angle of repose $\tan^{-1} h/r$	Average value of angle of repose
Ratio 1	1.23 1.24 1.24 1.24 1.23	3 3.06 3.08 3.04 3.04	1.5 1.53 1.54 1.52 1.52	39.35 39.02 38.84 39.21 38.98	39.08
Ratio 2	1.28 1.28 1.22 1.23 1.23	3.22 3.24 3.1 3.06 3.04	1.61 1.62 1.55 1.53 1.52	38.49 38.31 38.21 38.79 38.98	38.56
Ratio 3	1.25 1.25 1.25 1.24 1.23	3.2 3.22 3.24 3.24 3.2	1.6 1.61 1.62 1.62 1.6	37.99 37.83 37.65 37.43 37.55	37.69
Ratio 4	1.24 1.24 1.23 1.24 1.23	3.26 3.28 3.24 3.2 3.3	1.63 1.64 1.62 1.6 1.65	37.26 37.09 37.21 37.78 36.87	37.24
Ratio 5	1.24 1.23 1.23 1.24 1.23	3.3 3.32 3.3 3.28 3.3	1.65 1.66 1.65 1.64 1.65	36.92 36.54 36.70 37.09 36.70	36.79

By plotting percentage ratio of zinc stearate in X-axis and respected angle of repose in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, angle of repose of any set of excipients and APIs can be achieved.

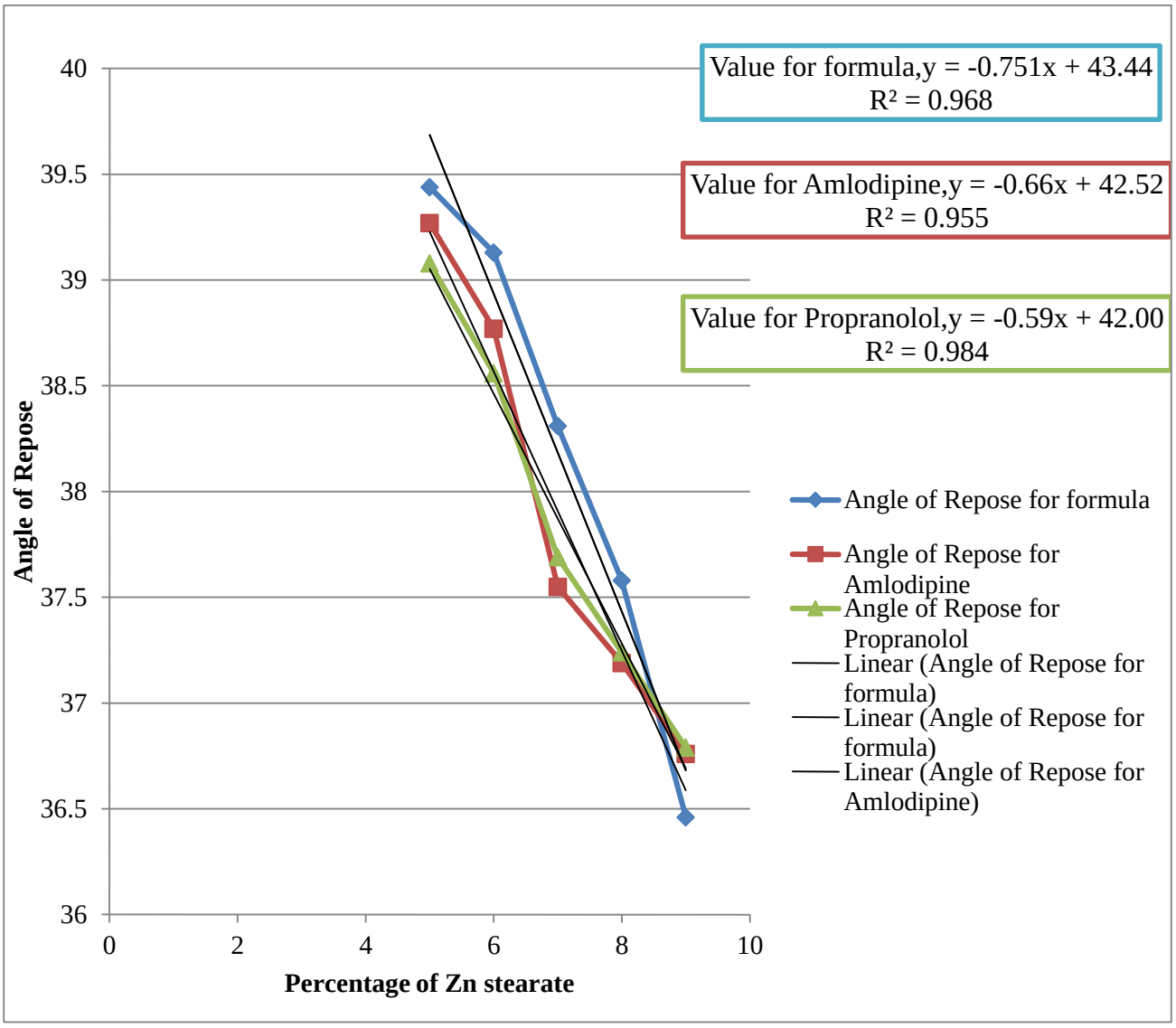

Figure 4.3: A percentage ratio of zinc stearate versus Angle of Repose graph

4.1.1.2 Calculation of excipients and APIs for Formula 2

The flow property of excipients and APIs were measured by calculating their Carr's index, Hausner ratio and angle of repose. For calculating Carr's index and Hausner ratio, their individual bulk volume and tapped volume were measured five times and the average value was taken. The observed value is given below:

4.7 Table: Values of Carr's Index and Hausner Ratio of excipients for Formula 2

Ratio	Bulk volume, V_o (ml)	Most acceptable bulk volume, V_o (ml)	Tapped volume, V_f (ml)	Most acceptable tapped volume, V_f (ml)	Hausner ratio (V_o/V_f)	Carr's index $100x\{(V_o-V_f)/V_f\}$
Ratio 1	9.2 9.5 9.5 9.4 9.4	9.5	7.5 7.3 7.3 7.8 7.6	7.3	1.30	30.14
Ratio 2	8.1 8.3 8.3 8.6 9	9	7.2 7.1 7.4 7.3 7.2	7.1	1.27	26.76
Ratio 3	8.1 8.3 8.3 8.6 9	9	7.2 7.1 7.4 7.3 7.2	7.1	1.27	26.76
Ratio 4	9.8 9.5 9.6 9.8 9.8	9.8	7.8 8 8.1 8 8	7.8	1.26	25.64
Ratio 5	8.7 8.8 8.8 8 9	9	7.9 8.1 7.5 7.5 7.7	7.5	1.2	20

4.8 Table: Values of Carr's Index and Hausner Ratio of excipients with API (Amlodipine) for Formula 2

Ratio	Bulk volume, V_o (ml)	Most acceptable bulk volume, V_o (ml)	Tapped volume, V_f (ml)	Most acceptable tapped volume, V_f (ml)	Hausner ratio (V_o/V_f)	Carr's index $100x\{(V_o-V_f)/V_f\}$
Ratio 1	3.9 4 4 4 4	4	3.1 3.1 3 3 3	3	1.33	33.33
Ratio 2	3.8 4.1 3.9 3.9 3.9	4.1	3.1 3.2 3.2 3.2 3.1	3.1	1.32	32.26
Ratio 3	3.8 4.1 3.9 3.9 3.9	4.1	3.1 3.2 3.2 3.2 3.1	3.1	1.32	32.26
Ratio 4	3.9 4 4 3.9 3.7	4	3.1 3.2 3.2 3.1 3.1	3.1	1.29	29.03
Ratio 5	4 4 4 3.8 3.8	4	3.3 3.2 3.2 3.2 3.2	3.2	1.25	25.81

4.9 Table: Values of Carr's Index and Hausner Ratio of excipients with API (Propranolol) for Formula 2

Ratio	Bulk volume, V_o (ml)	Most acceptable bulk volume, V_o (ml)	Tapped volume, V_f (ml)	Most acceptable tapped volume, V_f (ml)	Hausner ratio (V_o/V_f)	Carr's index $100x\{(V_o-V_f)/V_f\}$
Ratio 1	4 4 4.1 4.1 4.1	4.1	3.1 3.3 3.2 3.3 3.1	3.1	1.32	32.26
Ratio 2	4 4 4.1 4.1 4.1	4.1	3.1 3.2 3.2 3.1 3.1	3.1	1.32	32.26
Ratio 3	3.9 4 4 4 4	4	3.1 3.1 3.2 3.1 3.2	3.1	1.29	29.03
Ratio 4	4 4 4 3.8 3.8	4	3.3 3.2 3.2 3.2 3.2	3.2	1.25	25.81
Ratio 5	4 4 4 3.8 3.8	4	3.3 3.2 3.2 3.2 3.2	3.2	1.25	25.81

By plotting percentage ratio of zinc stearate in X-axis and respected Carr's index in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, Carr's index of any set of excipients and APIs can be achieved.

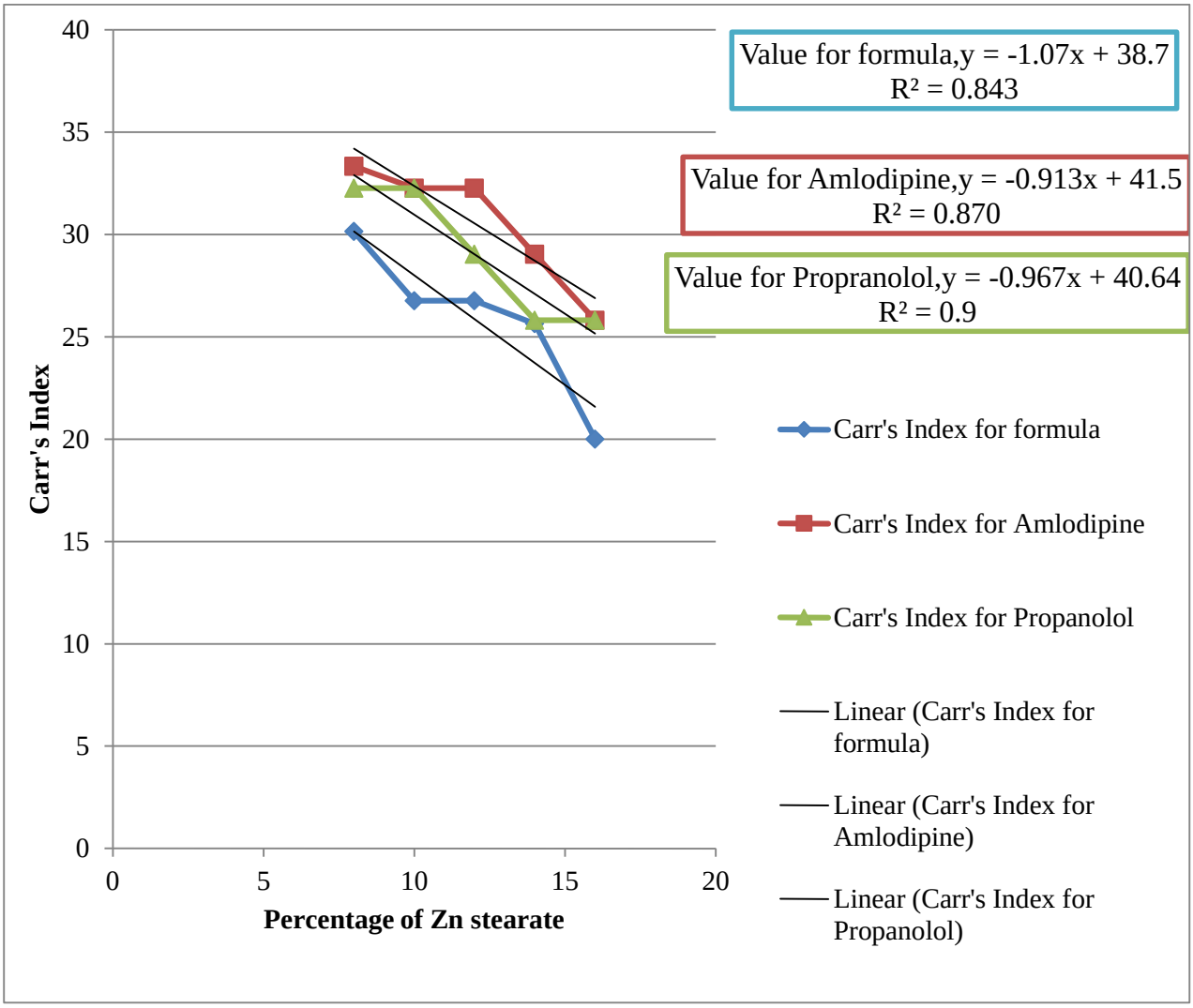

Figure 4.4: A percentage ratio of zinc stearate versus Carr's index graph

By plotting percentage ratio of zinc stearate in X-axis and respected Hausner ratio in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, Hausner ratio of any set of excipients and APIs can be achieved.

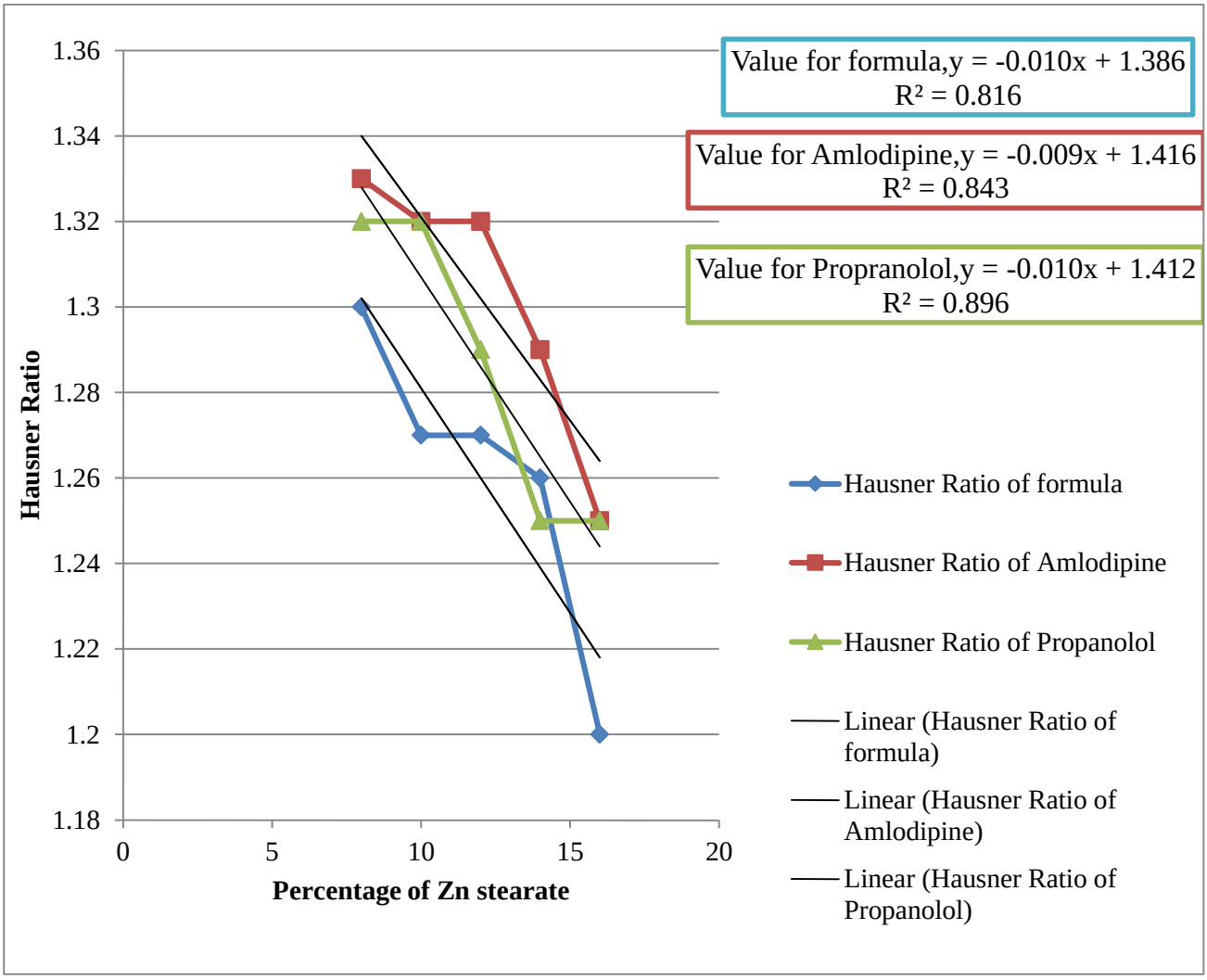

Figure 4.5: A percentage ratio of zinc stearate versus Hausner ratio graph

The angle of repose of Formula 2 was calculated by their cone height and radius which were measured five times and the average value was taken. The observed value is given below:

4.10Table: Value of Angle of Repose of excipients for Formula 2

Ratio	Height of the pile, h (cm)	Diameter of the pile, 2r (cm)	Radius of the pile, r (cm)	Angle of repose $\tan^{-1} h/r$	Average value of angle of repose
Ratio 1	1.6	3.86	1.93	39.65	
	1.6	3.9	1.95	39.37	
	1.6	3.82	1.91	39.95	39.13
	1.6	3.98	1.99	38.57	
	1.6	4.08	2.04	38.11	
Ratio 2	1.58	4.06	2.03	37.89	
	1.59	4.1	2.05	37.79	
	1.58	4.16	2.08	37.22	37.58
	1.58	4.18	2.09	37.08	
	1.59	4.08	2.04	37.93	
Ratio 3	1.5	4.07	2.035	36.39	
	1.45	3.98	1.99	36.079	
	1.5	4.02	2.01	36.73	36.46
	1.51	4.04	2.02	36.78	
	1.5	4.08	2.04	36.33	
Ratio 4	1.39	3.94	1.97	35.2	
	1.41	4.04	2.02	34.92	
	1.4	4	2	34.99	34.88
	1.4	4.06	2.03	34.59	
	1.4	4.04	2.02	34.72	
Ratio 5	1.4	4.08	2.04	34.46	
	1.41	4.12	2.06	34.39	
	1.4	4.1	2.05	34.33	34.416
	1.42	4.18	2.09	34.19	
	1.42	4.1	2.05	34.71	

4.11Table: Values of Angle of repose of excipients with API (Amlodipine) for Formula 2

Ratio	Height of the pile, h (cm)	Diameter of the pile, 2r (cm)	Radius of the pile, r (cm)	Angle of repose $\tan^{-1} h/r$	Average value of Angle of Repose
Ratio 1	1.28 1.28 1.22 1.23 1.23	3.22 3.24 3.1 3.06 3.04	1.61 1.62 1.55 1.53 1.52	38.49 38.31 38.21 38.79 38.98	38.56
Ratio 2	1.25 1.25 1.25 1.24 1.23	3.2 3.22 3.24 3.24 3.2	1.6 1.61 1.62 1.62 1.6	37.99 37.83 37.65 37.43 37.55	37.69
Ratio 3	1.24 1.23 1.23 1.24 1.23	3.3 3.32 3.3 3.28 3.3	1.65 1.66 1.65 1.64 1.65	36.92 36.54 36.70 37.09 36.70	36.79
Ratio 4	1.31 1.25 1.25 1.26 1.28	3.52 3.52 3.54 3.52 3.52	1.76 1.76 1.77 1.76 1.76	36.66 35.38 35.23 35.59 36.02	35.78
Ratio 5	1.2 1.21 1.22 1.21 1.22	3.52 3.52 3.5 3.5 3.48	1.76 1.76 1.75 1.75 1.74	34.29 34.50 34.88 34.66 35.03	34.67

4.12 Table: Values of Angle of repose of excipients with API (Propranolol) for Formula 2

Ratio	Height of the pile, h (cm)	Diameter of the pile, 2r (cm)	Radius of the pile, r (cm)	Angle of repose $\tan^{-1} h/r$	Average value of angle of repose
Ratio 1	1.21 1.23 1.23 1.24 1.21	3.04 3.04 3.06 3.06 3.04	1.52 1.52 1.53 1.53 1.52	38.52 38.98 38.79 39.02 38.52	38.77
Ratio 2	1.24 1.24 1.23 1.23 1.23	3.22 3.24 3.24 3.3 3.28	1.61 1.62 1.62 1.65 1.64	37.60 37.43 37.21 36.87 36.86	37.19
Ratio 3	1.23 1.24 1.23 1.24 1.23	3.3 3.32 3.32 3.3 3.32	1.65 1.66 1.66 1.65 1.66	36.87 36.73 36.54 36.92 36.73	36.76
Ratio 4	1.31 1.25 1.25 1.26 1.28	3.52 3.52 3.54 3.52 3.52	1.76 1.76 1.77 1.76 1.76	36.66 35.38 35.23 35.59 36.02	35.78
Ratio 5	1.2 1.21 1.22 1.21 1.22	3.52 3.52 3.5 3.5 3.48	1.76 1.76 1.75 1.75 1.74	34.29 34.50 34.88 34.66 35.03	34.67

By plotting percentage ratio of zinc stearate in X-axis and respected angle of repose in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, angle of repose of any set of excipients and APIs can be achieved.

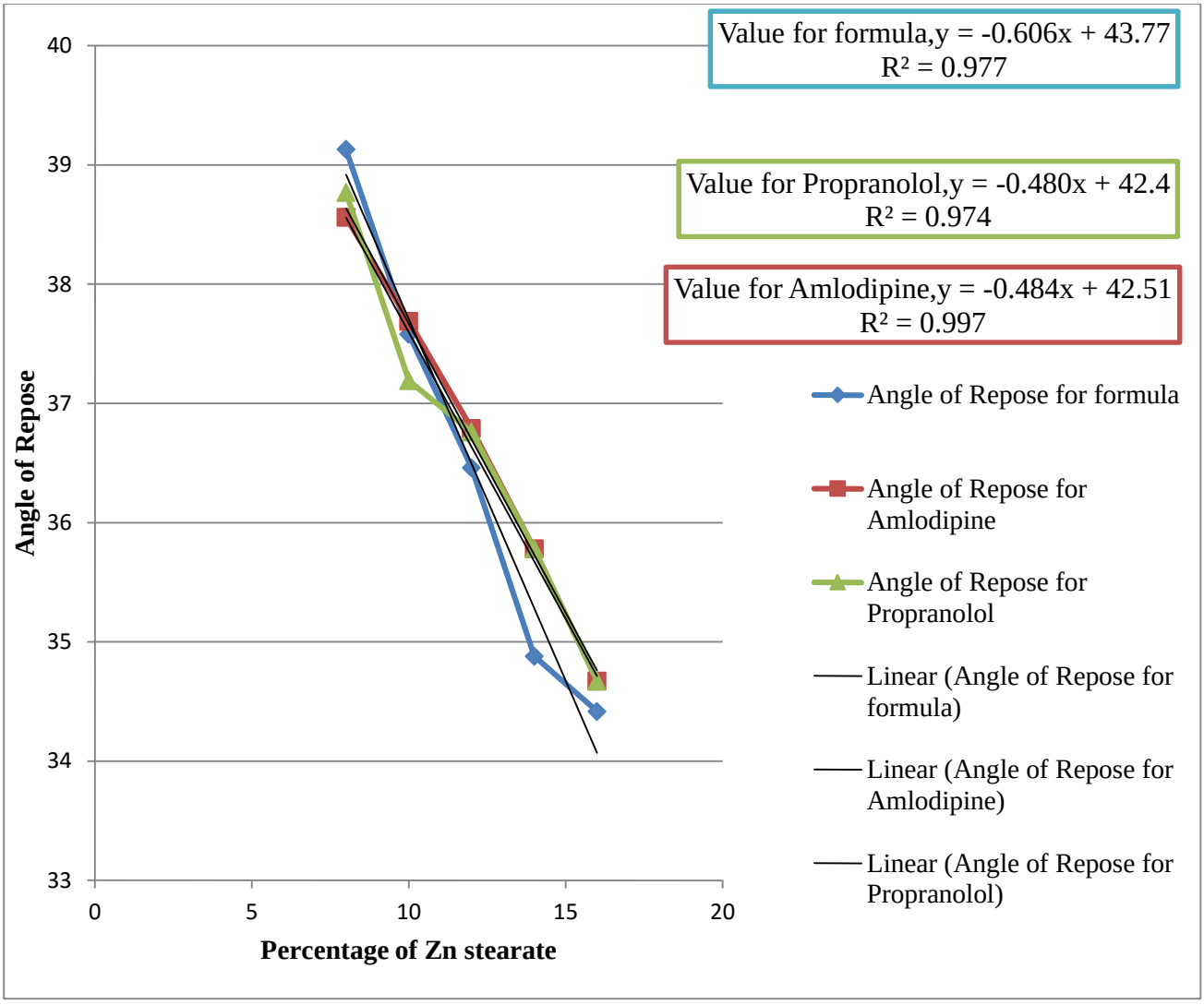

Figure 4.6: A percentage ratio of zinc stearate versus Angle of Repose graph

4.1.1.3 Calculation of excipients and APIs for Formula 3

The flow property of excipients and APIs were measured by calculating their Carr's index, Hausner ratio and angle of repose. For calculating Carr's index and Hausner ratio, their individual bulk volume and tapped volume were measured five times and the average value was taken. The observed value is given below:

4.13 Table: Values of Carr's Index and Hausner Ratio of excipients for Formula 3

Ratio	Bulk volume, V_o (ml)	Most acceptable bulk volume, V_o (ml)	Tapped volume, V_f (ml)	Most acceptable tapped volume, V_f (ml)	Hausner ratio (V_o/V_f)	Carr's index $100x\{(V_o-V_f)/V_f\}$
Ratio 1	9.2 8.8 9.2 8 9	9.2	7.1 7.2 7.1 7.1 7.2	7.1	1.29	29.58
Ratio 2	9.8 9.8 10 9.9 10	10	7.8 7.9 8 8.1 8	7.8	1.28	28.21
Ratio 3	9 9 9 8.7 9	9	7.2 7.3 7.1 7.1 7.2	7.1	1.27	26.76
Ratio 4	9.8 9.5 9.8 9.8 9.6	9.8	7.8 7.9 8 8 8.1	7.8	1.26	25.64
Ratio 5	9 8.6 8.5 8.6 9	9	7.5 7.8 7.8 8 7.5	7.5	1.2	20

4.14 Table: Values of Carr's Index and Hausner Ratio of excipients with API (Amlodipine) for Formula 3

Ratio	Bulk volume, V_o (ml)	Most acceptable bulk volume, V_o (ml)	Tapped volume, V_f (ml)	Most acceptable tapped volume, V_f (ml)	Hausner ratio (V_o/V_f)	Carr's index $100x\{(V_o-V_f)/V_f\}$
Ratio 1	4 4 3.9 3.9 4	4	3 3.1 3.1 3.1 3	3	1.33	33.33
Ratio 2	3.9 3.9 3.8 3.8 3.8	3.9	3 3 3 3.2 3.2	3	1.3	30
Ratio 3	4 4 3.9 3.9 3.9	4	3.2 3.2 3.2 3.2 3.1	3.1	1.29	29.03
Ratio 4	4 4 4.1 4.1 4.1	4.1	3.2 3.2 3.2 3.2 3.3	3.2	1.28	28.13
Ratio 5	3.9 3.9 3.8 3.9 4	4	3.3 3.2 3.3 3.2 3.3	3.2	1.25	25.81

4.15 Table: Values of Carr's Index and Hausner Ratio of excipients with API (Propranolol) for Formula 3

Ratio	Bulk volume, V_o (ml)	Most acceptable bulk volume, V_o (ml)	Tapped volume, V_f (ml)	Most acceptable tapped volume, V_f (ml)	Hausner ratio (V_o/V_f)	Carr's index $100x\{(V_o-V_f)/V_f\}$
Ratio 1	3.9 3.9 3.8 3.8 3.8	3.9	3 3 3 3.2 3.2	3	1.3	30
Ratio 2	4 4 3.9 3.9 3.9	4	3.2 3.2 3.2 3.2 3.1	3.1	1.29	29.03
Ratio 3	4 4 3.9 3.9 4	4	3.1 3.2 3.1 3.1 3.1	3.1	1.29	29.03
Ratio 4	4.1 4.1 3.9 3.9 3.9	4.1	3.3 3.3 3.2 3.2 3.2	3.2	1.28	28.13
Ratio 5	3.9 3.9 3.8 3.9 4	4	3.3 3.3 3.4 3.2 3.2	3.2	1.25	25.81

By plotting percentage ratio of zinc stearate in X-axis and respected Carr's index in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, Carr's index of any set of excipients and APIs can be achieved.

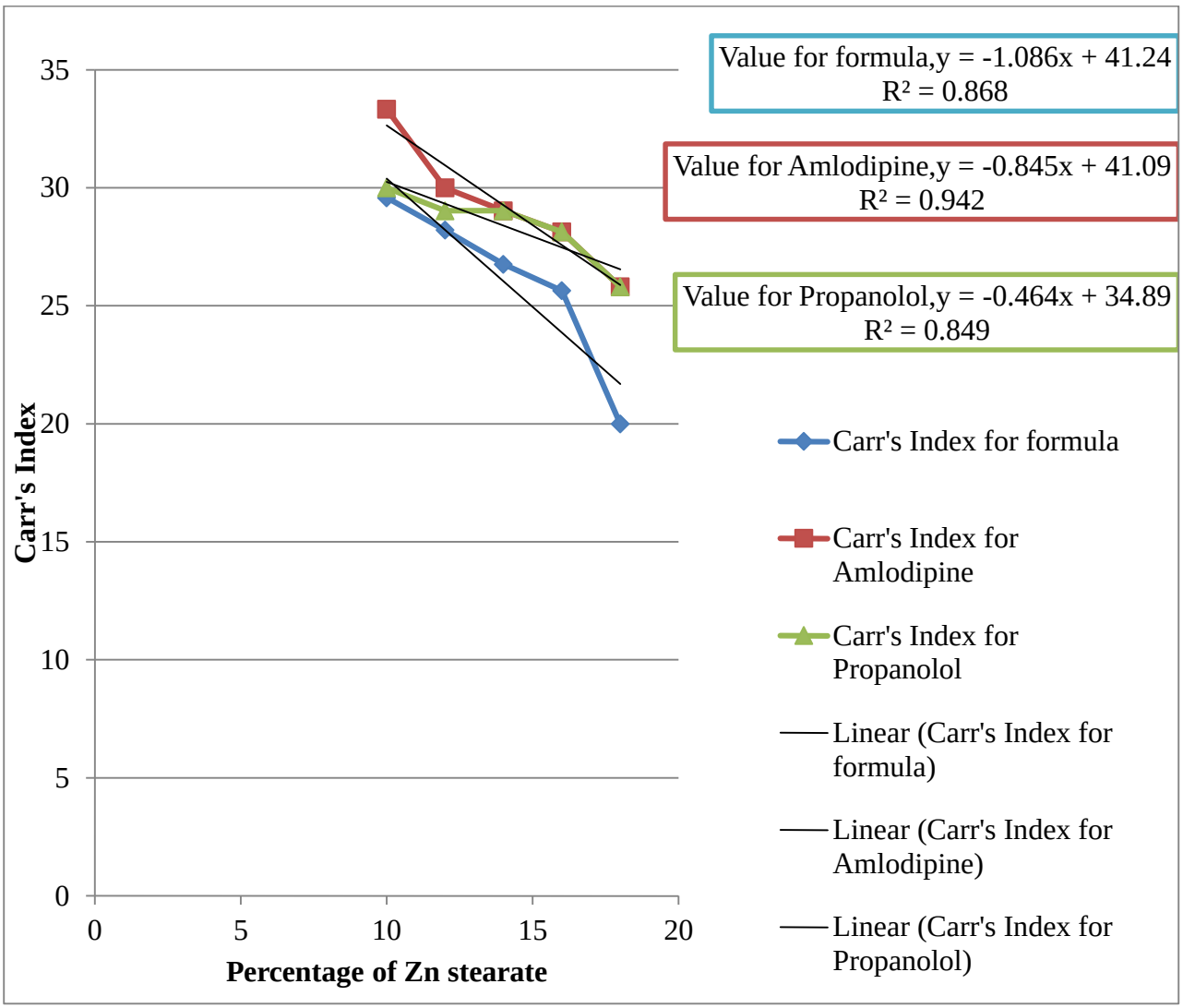

Figure 4.7: A percentage ratio of zinc stearate versus Carr's index graph

By plotting percentage ratio of zinc stearate in X-axis and respected Hausner ratio in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, Hausner ratio of any set of excipients and APIs can be achieved.

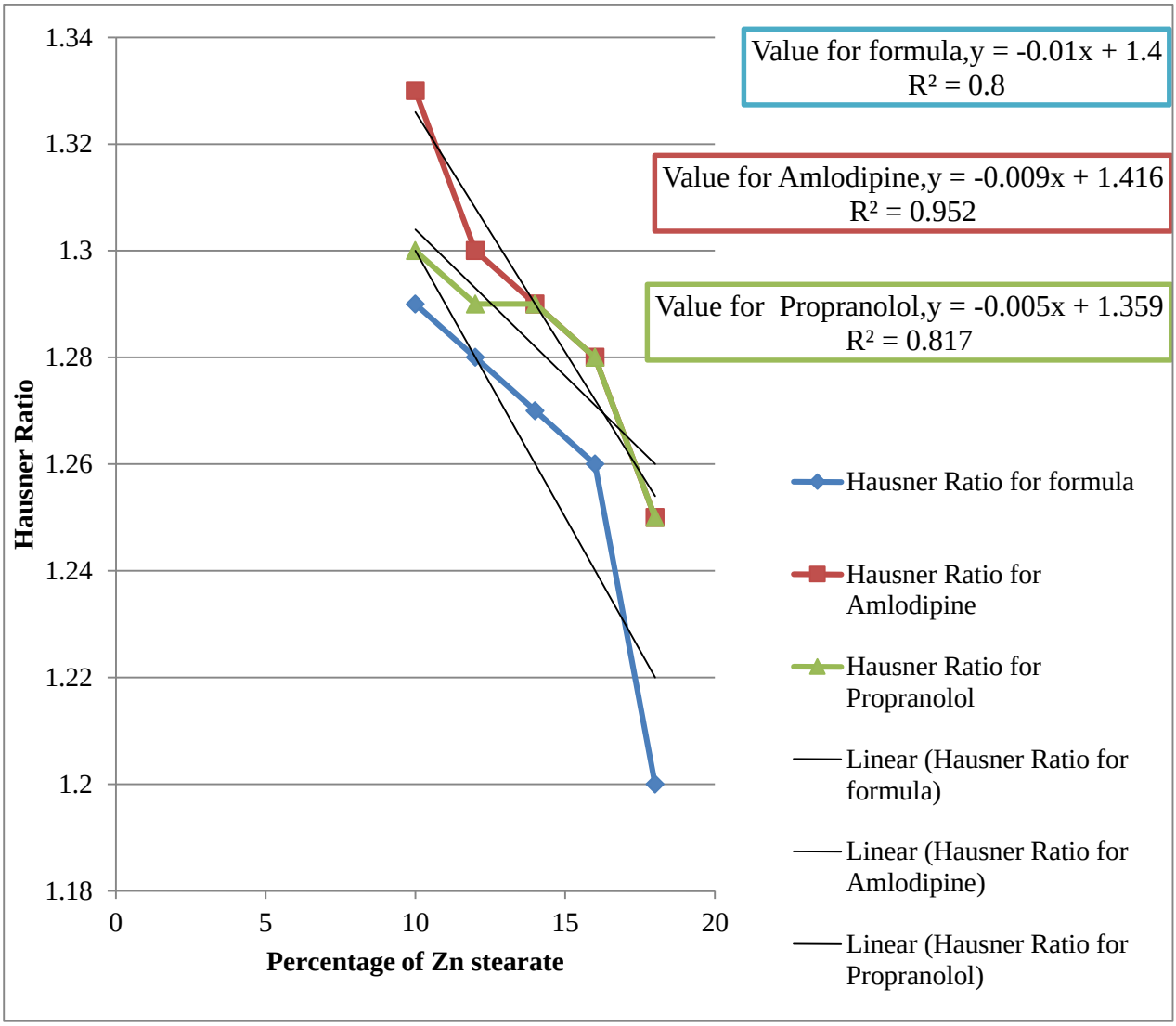

Figure 4.8: A percentage ratio of zinc stearate versus Hausner ratio graph

The angle of repose of Formula 3 was calculated by their cone height and radius which were measured five times and the average value was taken. The observed value is given below:

4.16 Table: Value of Angle of Repose of excipients for Formula 3

Ratio	Height of the pile, h (cm)	Diameter of the pile, 2r (cm)	Radius of the pile, r (cm)	Angle of repose $\tan^{-1} h/r$	Average value of Angle of Repose
Ratio 1	1.58 1.59 1.58 1.58 1.59	4.06 4.1 4.16 4.18 4.08	2.03 2.05 2.08 2.09 2.04	37.89 37.79 37.22 37.08 37.93	37.58
Ratio 2	1.45 1.5 1.5 1.51 1.5	3.98 4.02 4.08 4.04 4.07	1.99 2.01 2.04 2.02 2.035	36.08 36.73 36.33 36.78 36.39	36.46
Ratio 3	1.39 1.41 1.4 1.4 1.4	3.94 4.04 4 4.04 4.06	1.97 2.02 2 2.02 2.03	35.2 34.92 34.99 34.72 34.59	34.88
Ratio 4	1.4 1.6 1.4 1.5 1.41	4.62 5.26 4.68 4.82 4.68	2.31 2.63 2.34 2.41 2.34	31.21 31.31 30.89 31.89 31.07	31.27
Ratio 5	1.2 1.2 1.22 1.21 1.23	4.362 4.34 4.34 4.36 4.34	2.18 2.17 2.17 2.18 2.17	28.83 28.94 29.35 29.14 29.55	29.16

4.17Table: Values of Angle of repose of excipients with API (Amlodipine) for Formula 3

Ratio	Height of the pile, h (cm)	Diameter of the pile, 2r (cm)	Radius of the pile, r (cm)	Angle of repose $\tan^{-1} h/r$	Average value of Angle of Repose
Ratio 1	1.25 1.25 1.25 1.24 1.23	3.2 3.22 3.24 3.24 3.2	1.6 1.61 1.62 1.62 1.6	37.99 37.83 37.65 37.43 37.55	37.69
Ratio 2	1.23 1.24 1.23 1.24 1.23	3.3 3.32 3.32 3.3 3.32	1.65 1.66 1.66 1.65 1.66	36.87 36.73 36.54 36.92 36.73	36.76
Ratio 3	1.31 1.25 1.25 1.26 1.28	3.52 3.52 3.54 3.52 3.52	1.76 1.76 1.77 1.76 1.76	36.66 35.38 35.23 35.59 36.02	35.78
Ratio 4	1.2 1.21 1.22 1.21 1.22	3.52 3.52 3.5 3.5 3.48	1.76 1.76 1.75 1.75 1.74	34.29 34.50 34.88 34.66 35.03	34.67
Ratio 5	1.2 1.21 1.2 1.21 1.2	3.54 3.56 3.56 3.58 3.58	1.77 1.78 1.78 1.79 1.78	34.13 34.20 33.99 34.06 33.99	34.07

4.18 Table: Values of Angle of repose of excipients with API (Propranolol) for Formula 3

Ratio	Height of the pile, h (cm)	Diameter of the pile, 2r (cm)	Radius of the pile, r (cm)	Angle of repose $\tan^{-1} h/r$	Average value of Angle of Repose
Ratio 1	1.25 1.25 1.25 1.24 1.23	3.2 3.22 3.24 3.24 3.2	1.6 1.61 1.62 1.62 1.6	37.99 37.83 37.65 37.43 37.55	37.69
Ratio 2	1.24 1.23 1.23 1.24 1.23	3.3 3.32 3.3 3.28 3.3	1.65 1.66 1.65 1.64 1.65	36.92 36.54 36.70 37.09 36.70	36.79
Ratio 3	1.31 1.25 1.25 1.26 1.28	3.52 3.52 3.54 3.52 3.52	1.76 1.76 1.77 1.76 1.76	36.66 35.38 35.23 35.59 36.02	35.78
Ratio 4	1.2 1.21 1.22 1.21 1.22	3.52 3.52 3.5 3.5 3.48	1.76 1.76 1.75 1.75 1.74	34.29 34.50 34.88 34.66 35.03	34.67
Ratio 5	1.2 1.21 1.2 1.21 1.2	3.54 3.56 3.56 3.58 3.58	1.77 1.78 1.78 1.79 1.78	34.13 34.20 33.99 34.06 33.99	34.07

By plotting percentage ratio of zinc stearate in X-axis and respected angle of repose in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, angle of repose of any set of excipients and APIs can be achieved.

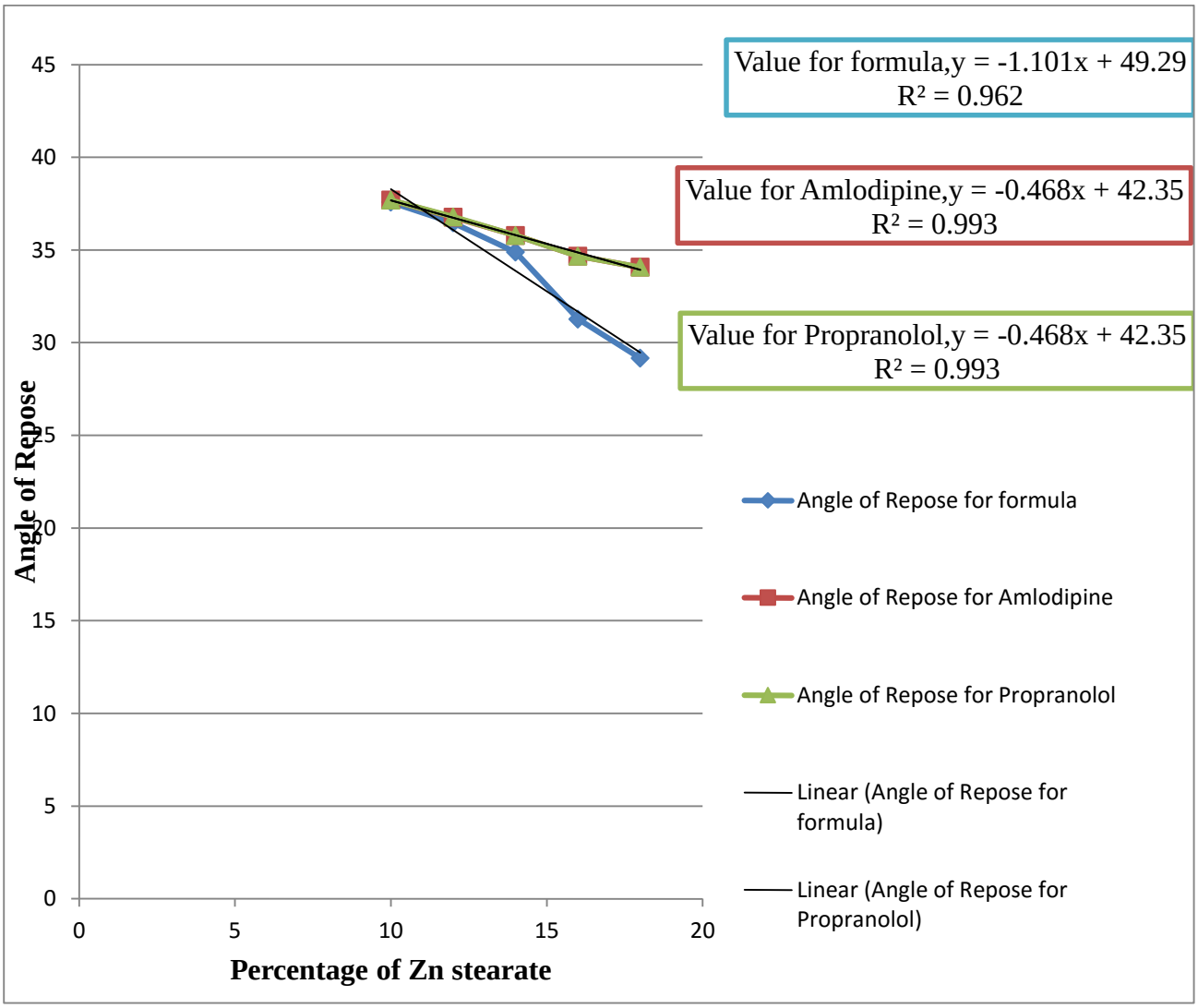

Figure 4.9: A percentage ratio of zinc stearate versus Angle of repose graph

4.1.1.4 Calculation of excipients and APIs for Formula 4

The flow property of excipients and APIs were measured by calculating their Carr's index, Hausner ratio and angle of repose. For calculating Carr's index and Hausner ratio, their individual bulk volume and tapped volume were measured five times and the average value was taken. The observed value is given below:

4.19Table: Values of Carr's Index and Hausner Ratio of excipients for Formula 4

Ratio	Bulk volume, V_o (ml)	Most acceptable bulk volume, V_o (ml)	Tapped volume, V_f (ml)	Most acceptable tapped volume, V_f (ml)	Hausner ratio (V_o/V_f)	Carr's index $100x\{(V_o-V_f)/V_f\}$
Ratio 1	9.2 9.5 9.5 9.4 9.4	9.5	7.5 7.3 7.3 7.8 7.6	7.3	1.30	30.14
Ratio 2	9.2 9.2 9.5 9.5 9.5	9.5	7.6 7.3 7.3 7.6 7.6	7.3	1.30	30.14
Ratio 3	9.2 8.8 9.2 8 9	9.2	7.1 7.2 7.1 7.1 7.2	7.1	1.29	29.58
Ratio 4	9.8 9.8 10 9.9 10	10	7.8 7.9 8 8.1 8	7.8	1.28	28.21
Ratio 5	8.7 8.8 8.8 8 9	9	7.1 7.5 7.1 7.2 7.1	7.1	1.27	26.76

4.20Table: Values of Carr's Index and Hausner Ratio of excipients with API (Amlodipine) for Formula 4

Ratio	Bulk volume, V_o (ml)	Most acceptable bulk volume, V_o (ml)	Tapped volume, V_f (ml)	Most acceptable tapped volume, V_f (ml)	Hausner ratio (V_o/V_f)	Carr's index $100x\{(V_o-V_f)/V_f\}$
Ratio 1	3.9 3.8 4 4 4	4	3.2 3 3.2 3.2 3	3	1.33	33.33
Ratio 2	4 4 3.6 3.7 3.6	4	3 3.2 3.2 3.1 3.1	3	1.33	33.33
Ratio 3	3.8 3.8 4.1 4 3.9	4.1	3.2 3.2 3.3 3.2 3.3	3.2	1.28	33.33
Ratio 4	4.1 4 3.6 3.7 3.6	4.1	3.2 3.3 3.2 3.2 3.3	3.2	1.28	28.13
Ratio 5	3.8 3.8 3.8 3.9 3.9	3.9	3.2 3.1 3.2 3.3 3.2	3.1	1.25	25.81

4.21Table: Values of Carr's Index and Hausner Ratio of excipients with API (Propranolol) for Formula 4

Ratio	Bulk volume, V_o (ml)	Most acceptable bulk volume, V_o (ml)	Tapped volume, V_f (ml)	Most acceptable tapped volume, V_f (ml)	Hausner ratio (V_o/V_f)	Carr's index $100x\{(V_o-V_f)/V_f\}$
Ratio 1	3.9 3.8 3.9 3.9 3.9	3.9	3.2 3 3.2 3.2 3	3	1.3	30
Ratio 2	3.9 3.9 4 3.9 3.8	4	3.1 3.2 3.2 3.1 3.1	3.1	1.29	29.03
Ratio 3	3.9 3.8 4.1 4.1 3.9	4.1	3.2 3.2 3.3 3.3 3.2	3.2	1.28	28.13
Ratio 4	3.9 3.9 3.6 3.7 3.6	3.9	3.1 3.1 3.2 3.1 3.2	3.1	1.25	25.81
Ratio 5	3.8 3.8 3.8 3.9 3.9	3.9	3.2 3.1 3.2 3.3 3.2	3.1	1.25	25.81

By plotting percentage ratio of zinc stearate in X-axis and respected Carr's index in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, Carr's index of any set of excipients and APIs can be achieved.

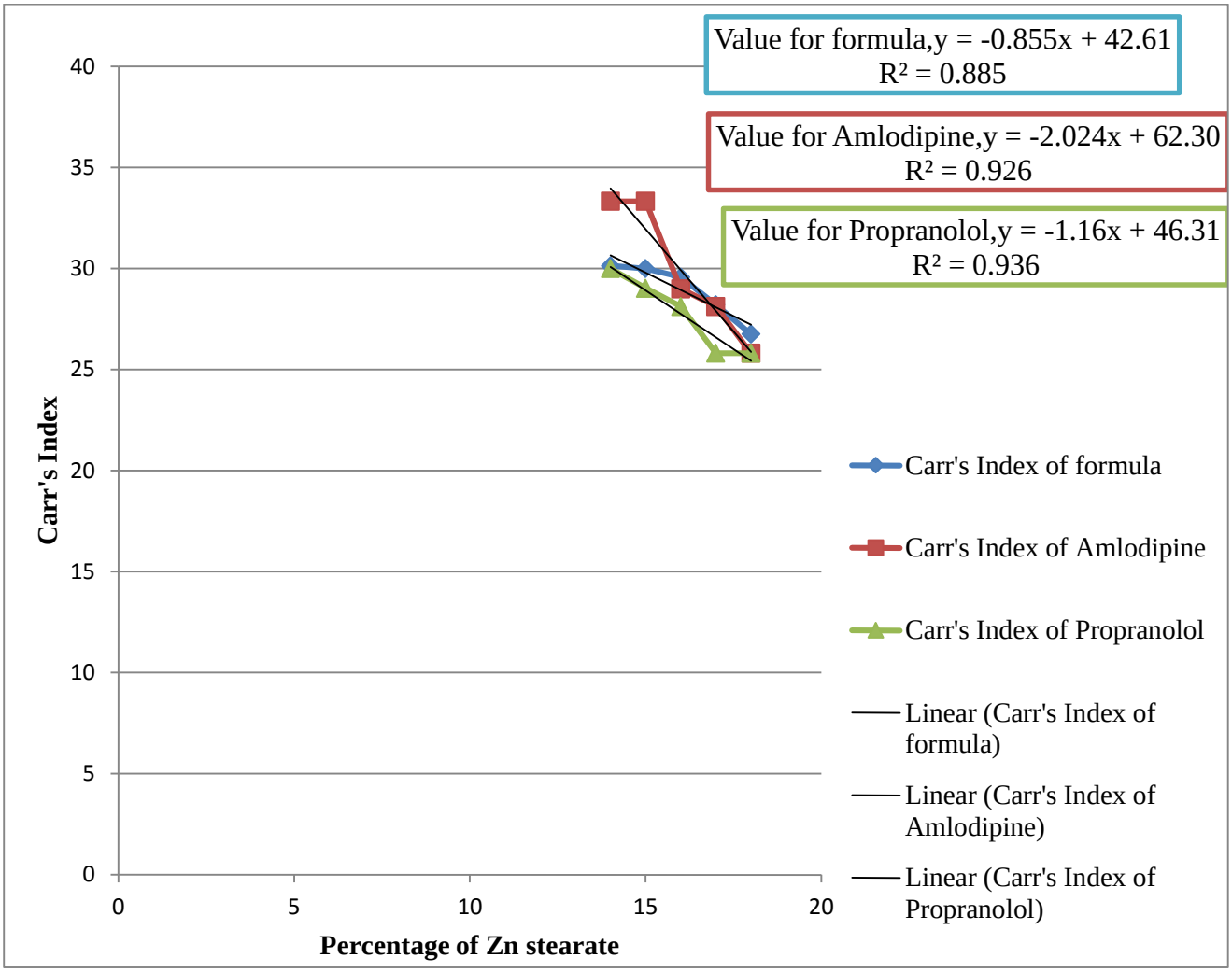

Figure 4.10: A percentage ratio of zinc stearate versus Carr's Index graph

By plotting percentage ratio of zinc stearate in X-axis and respected Hausner ratio in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, Hausner ratio of any set of excipients and APIs can be achieved.

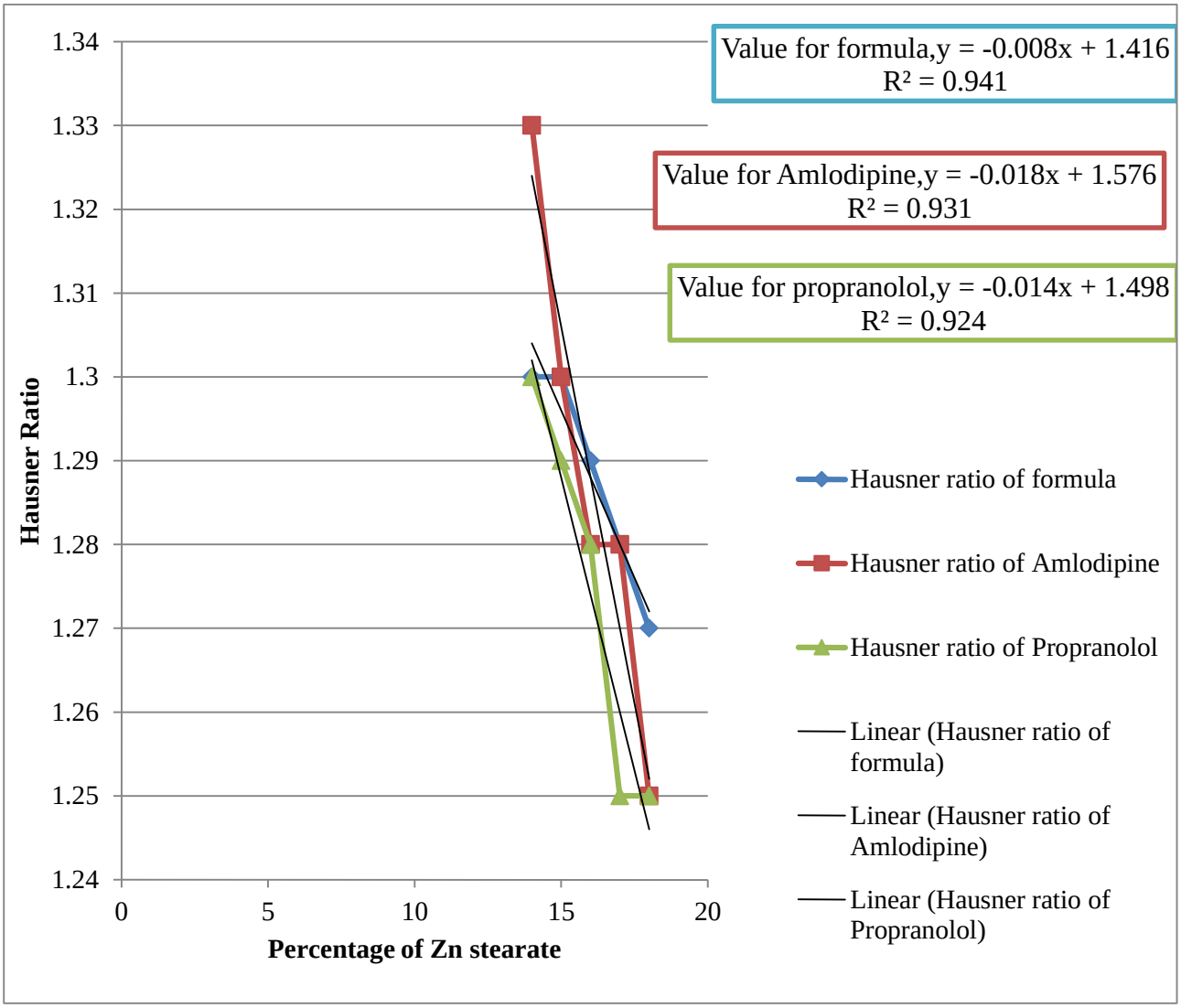

Figure 4.11: A percentage ratio of zinc stearate versus Hausner ratio graph

The angle of repose of Formula 2 was calculated by their cone height and radius which were measured five times and the average value was taken. The observed value is given below:

4.22Table: Value of Angle of Repose of excipients for Formula 4

Ratio	Height of the pile, h (cm)	Diameter of the pile, 2r (cm)	Radius of the pile, r (cm)	Angle of repose $\tan^{-1} h/r$	Average value of Angle of Repose
Ratio 1	1.45 1.5 1.5 1.51 1.5	3.98 4.02 4.08 4.04 4.07	1.99 2.01 2.04 2.02 2.035	36.08 36.73 36.33 36.78 36.39	36.46
Ratio 2	1.39 1.41 1.4 1.4 1.4	3.94 4.04 4 4.04 4.06	1.97 2.02 2 2.02 2.03	35.2 34.92 34.99 34.72 34.59	34.88
Ratio 3	1.5 1.6 1.49 1.5 1.48	4.62 4.98 4.62 4.644 4.62	2.31 2.49 2.31 2.322 2.31	32.99 32.72 32.82 32.86 32.65	32.80
Ratio 4	1.4 1.6 1.4 1.5 1.41	4.62 5.26 4.68 4.82 4.68	2.31 2.63 2.34 2.41 2.34	31.21 31.31 30.89 31.89 31.07	31.27
Ratio 5	1.2 1.2 1.22 1.21 1.23	4.362 4.34 4.34 4.36 4.34	2.18 2.17 2.17 2.18 2.17	28.83 28.94 29.35 29.14 29.55	29.162

4.23Table: Value of Angle of Repose of excipients with API (Amlodipine) for Formula 4

Ratio	Height of the pile, h (cm)	Diameter of the pile, 2r (cm)	Radius of the pile, r (cm)	Angle of repose $\tan^{-1} h/r$	Average value of Angle of Repose
Ratio 1	1.23 1.24 1.23 1.24 1.23	3.3 3.32 3.32 3.3 3.32	1.65 1.66 1.66 1.65 1.66	36.87 36.73 36.54 36.92 36.73	36.76
Ratio 2	1.31 1.25 1.25 1.26 1.28	3.52 3.52 3.54 3.52 3.52	1.76 1.76 1.77 1.76 1.76	36.66 35.38 35.23 35.59 36.02	35.78
Ratio 3	1.2 1.21 1.2 1.21 1.2	3.54 3.56 3.56 3.58 3.56	1.77 1.78 1.78 1.79 1.78	34.13 34.20 33.99 34.06 33.99	34.07
Ratio 4	1.2 1.2 1.2 1.2 1.2	3.58 3.56 3.6 3.56 3.62	1.79 1.78 1.8 1.78 1.81	33.84 33.99 33.69 33.99 33.54	33.81
Ratio 5	1.2 1.2 1.22 1.21 1.23	4.362 4.34 4.34 4.36 4.34	2.18 2.17 2.17 2.18 2.17	28.83 28.94 29.35 29.14 29.55	29.162

4.24Table: Value of Angle of Repose of excipients with API (Propranolol) for Formula 4

Ratio	Height of the pile, h (cm)	Diameter of the pile, 2r (cm)	Radius of the pile, r (cm)	Angle of repose $\tan^{-1} h/r$	Average value of Angle of Repose
Ratio 1	1.24 1.23 1.23 1.24 1.23	3.3 3.32 3.3 3.28 3.3	1.65 1.66 1.65 1.64 1.65	36.92 36.54 36.70 37.09 36.70	36.79
Ratio 2	1.31 1.25 1.25 1.26 1.28	3.52 3.52 3.54 3.52 3.52	1.76 1.76 1.77 1.76 1.76	36.66 35.38 35.23 35.59 36.02	35.78
Ratio 3	1.2 1.21 1.2 1.21 1.2	3.54 3.56 3.56 3.58 3.58	1.77 1.78 1.78 1.79 1.78	34.13 34.20 33.99 34.06 33.99	34.07
Ratio 4	1.2 1.2 1.2 1.2 1.2	3.58 3.56 3.6 3.56 3.62	1.79 1.78 1.8 1.78 1.81	33.84 33.99 33.69 33.99 33.54	33.81
Ratio 5	1.2 1.2 1.22 1.21 1.23	4.362 4.34 4.34 4.36 4.34	2.18 2.17 2.17 2.18 2.17	28.83 28.94 29.35 29.14 29.55	29.16

By plotting percentage ratio of zinc stearate in X-axis and respected angle of repose in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, angle of repose of any set of excipients and APIs can be achieved.

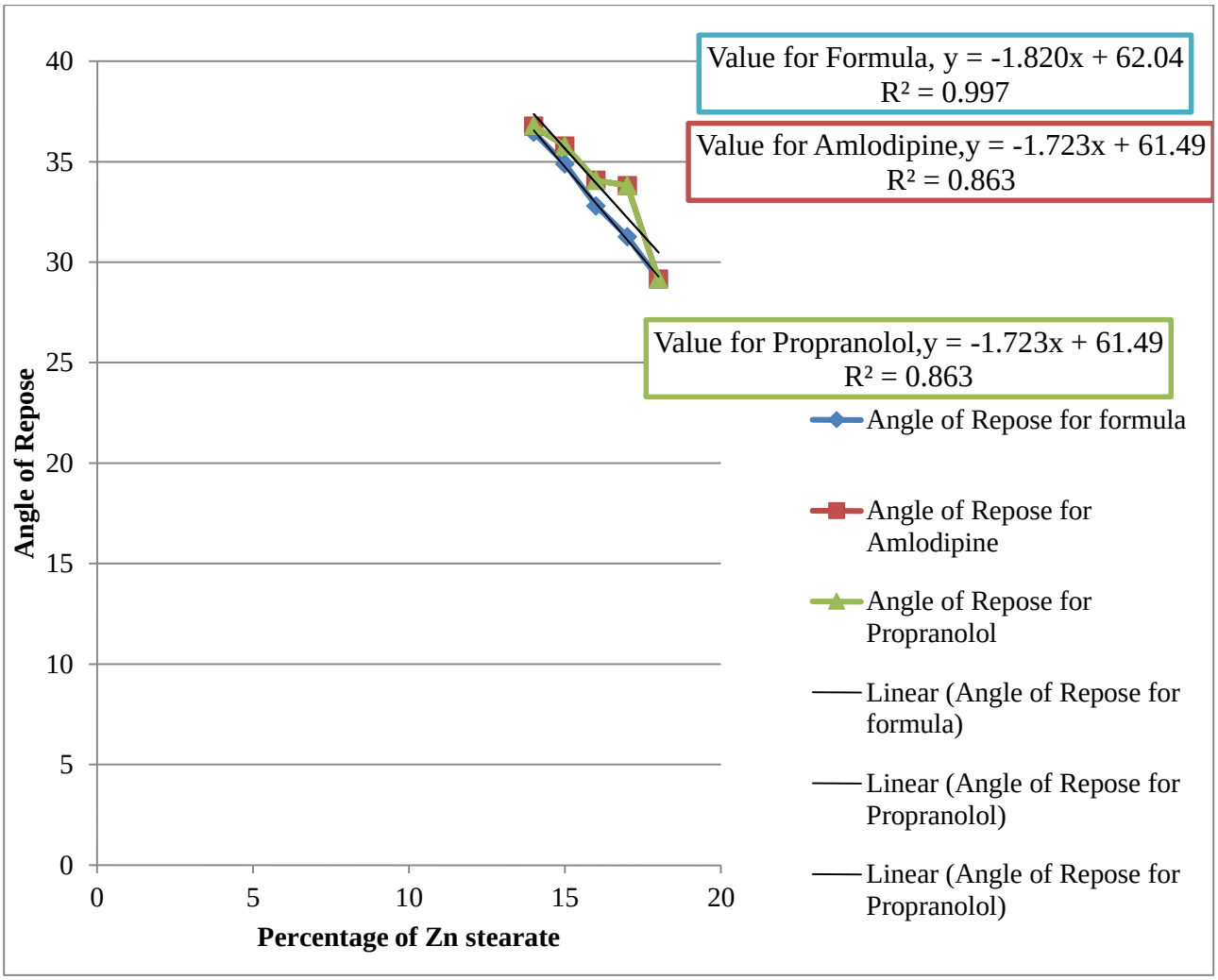

Figure 4.12: A percentage ratio of zinc stearate versus Angle of repose graph

Table 4.25: Carr's Index equations and best percentage with flow property

Formula	Equation and regression value	Best percentage of Zn stearate	Flow property according to USP29
F1	y=-1.601x+40.73, R^2=0.916	9	Poor
F1	y=-2.222x+42.45, R^2=0.891	9	Passable
F1	y=-1.468x+38.95, R^2=0.923	9	Passable
F2	y=-1.07x+38.7, R^2=0.843	16	Poor
F2	y=-0.913x+41.5, R^2=0.870	16	Poor
F2	y=-967x+40.64, R^2=0.9	16	Poor
F3	y=-1.086x+41.24, R^2=0.868	18	Fair
F3	y=-0.845x+41.09, R^2=0.942	18	Passable
F3	y=0.464x+34.89, R^2=0.849	18	Passable
F4	y=0.855x+42.61, R^2=0.885	18	Poor
F4	y=-2.024x+62.30, R^2=0.926	18	Poor
F4	y=-1.16x+46.31, R^2=0.936	18	Poor

Table 4.26: Hausner Ratio equations and best percentage with flow property

Formula	Equation and regression value	Best percentage of Zn stearate	Flow property according to USP29
F1	Y=-0.015x+1.399, R^2=0.892	8,9	Passable
F1	y=-0.022x+1.42, R^2=0.909	9	Fair
F1	y=-0.016x+1.396, R^2=0.941	9	Fair
F2	y=0.010x+1.386, R^2=0.816	16	Fair
F2	y=-0.009x+1.416, R^2=0.843	16	Fair
F2	y=-0.010x+1.412, R^2=0.896	14,16	Fair
F3	y=-0.01x+1.4, R^2=0.8	18	Fair
F3	y=-0.009x+0.416, R^2=0.952	18	Fair
F3	y=0.005x+1.359, R^2=0.817	18	Fair
F4	y=-0.008x+1.416, R^2=0.941	18	Passable
F4	y=-0.018x+1.576, R^2=0.931	18	Fair
F4	y=-0.014x+1.498, R^2=0.924	18	Far

Table4.27: Angle of Repose equations and best percentage with flow property

Formula	Equation and regression value	Best percentage of Zn stearate	Flow property according to USP29
F1	y=-0.751x+43.44, R^2=0.968	9	Fair
F1	y=-0.66x+42.52, R^2=0.955	9	Fair
F1	y=-0.59x+42.00, R^2=0.984	9	Fair
F2	y=-0.606x+43.77, R^2=0.977	16	Good
F2	y=-0.480x+42.4, R^2=0.974	16	Good
F2	y=-0.48x+42.51, R^2=0.997	16	Good
F3	y=-1.101x+49.29, R^2=0.962	18	Excellent
F3	y=-0.468x+42.35, R^2=0.993	18	Good
F3	y=-0.468x+42.35, R^2=0.993	18	Good
F4	y=-0.855x+42.61, R^2=0.885	18	Excellent
F4	y=-2.024x+62.30. R^2=0.926	18	Good
F4	y=-1.16x+46.31, R^2=0.936	18	Excellent

Chapter Five

DISCUSSION

5.1 Discussion

This work was proposed to determine flow properties of different set of pharmaceutical excipients with APIs. Different parameters to determine flow property such as Compressibility index, Hausner ratio, and angle of repose were observed. Individual flow property of the excipients was also determined. Many unique formulas were equipped by choosing various excipients from different classes. Different specific and justified ratio of antiadherents were mixed with those prepared formuls. APIs were also used for measuring the flow property. The study showed a wide range of deviation of flow property between different ratios of mixture. The values of Carr's index, Hausner ratio and angle of repose were plotted against the percentage ratios of antiadherents.In that experiment I had used Zn stearate as a antiadherent. From those graphs the straightline equation for each set of formula were obtained which can be used to predict the flow property of these formula with different set of pharmaceutical excipients with APIs while adding antiadherents in different ratio.

The research work had demonstrated that flow property of different set of formulas with APIs did not maintain the same rule. The variation of results observed between different parameters of measuring flow property such as Carr's index, Hausner ratio and angle of repose. In this chapter, the found result was compared with the established value of different flow property parameters. Variation of flow property of different set of formulas of excipients and APIs against variable ratio of different antiadherents was discussed below with some observed deviations.

- **In case of Formula-1,**

The Carr's Index and Hausner Ratio (Table 4.1, 4.2, 4.3 and Graph 4.1, 4.2) signified that, the values of Carr's Index and Hausner Ratio gradually decreased with the increased amount of Zn stearate.
The angle of repose (Table 4.4, 4.5, 4.6 and Graph 4.3) was also decreased gradually with the increased amount of Zn stearate.
It was stated that the lower the value of Carr's index, Hausner ratio and angle of repose, the better the flow property. After the addition of APIs the value of Carr's Index and Hausner Ratio didnot change drastically.
So for the Formula 1, the most desirable flow was obtained when the ratio of Zn stearate and formula-1 is 9%:91%.So it can be said that in that ratio the values of angle of repose lied in the fair range (Table 1.1).

- **In case of Formula-2,**

The Carr's Index and Hausner Ratio (Table 4.7, 4.8, 4.9 and Graph 4.4, 4.5) signified that, the values of Carr's Index and Hausner Ratio gradually decreased with the increased amount of Zn stearate.

The angle of repose (Table 4.10, 4.11, 4.12 and Graph 4.6) was also decreased gradually with the increased amount of Zn stearate.
According to obtained angle of repose values, the most desirable flow was obtained when the ratio of Zn stearate and formula 2 is 16%:84% which can be classified as 'good' flowing powder mixture.

- **In case of Formula-3**

The Carr's Index and Hausner Ratio (Table 4.13, 4.14, 4.15 and Graph 4.7, 4.8) signified that, the values of Carr's Index and Hausner Ratio gradually decreased with the increased amount of Zn stearate.
The angle of repose (Table 4.16, 4.17, 4.18 and Graph 4.9) was also decreased gradually with the increased amount of Zn stearate.
According to obtained angle of repose values,the most desirable flow was obtained when the ratio of Zn stearate and formula 2 was 18%:82% which can be classified as 'excellent' flowing powder mixture. But in formula 3 when the APIs were added angle of repose lied in good range.

- **In case of Formula-4**

The Carr's Index and Hausner Ratio (Table 4.19, 4.20, 4.21 and Graph 4.10, 4.11) signified that, the values of Carr's Index and Hausner Ratio gradually decreased with the increased amount of Zn stearate.
The angle of repose (Table 4.22, 4.23, 4.24 and Graph 4.12) was also decreased gradually with the increased amount of Zn stearate.
According to obtained angle of repose values, the most desirable flow was obtained when the ratio of Zn stearate and formula 2 is 18%:82% which can be classified as 'excellent' flowing powder mixture.

Chapter Six

CONCLUSION

6.1 Conclusion

Pharmaceutical excipients are considered as a vital part of any dosage form formulation. Without these ingredients directly compressible solid dosage formulation cannot proceed as it serves a variety of application and uses from the process of compression to bioavailability throughout the human body. For the process of tableting, the ingredients flowability is an important sector as powders have to pass through the hopper to the punching dyes. So the measurement of powder flow property is very necessary for any pharmaceutical industry or research sector.

In this research work we tried our best to determine the flow characteristics of mixture of excipients with different amounts of some selected excipients andAPIs. It can be stated that variation in amounts of excipients in the mixture showed a variation in the powder flow characteristics. Moreover, the plotted graphs and the equations for each set of formula were obtained which can be used to predict the flow property of those formulas with different ratio of antiadherents. This would help any future query about the flow property of any set of excipients with APIs with different ratios of antiadherents. For better result we should use more API but due to lack of time we only used two APIs to evaluate the flow property.

Overall this research work will be beneficial in formulation development of new drug product as well as this research work will be advantageous for Research & Development department of pharmaceutical company.

Chapter Seven

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7.1 REFERENCES

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