“Variation of Flow Property of Different Set of Formulas of Excipients Against Variable Ratio of Different Diluents”

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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, **Mahjabin Haque**, hereby declare that the dissertation entitled **"Variation of Flow Property of Different Set of Formulas of Excipients Against Variable Ratio of Different Diluents"** submitted by me to the Department of Pharmacy, East West University, in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Honors) is a confide record of original research work carried out by me under the supervision and guidance of **Md. Anisur Rahman**, Senior Lecturer, Dept. of Pharmacy, East West University.

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CERTIFICATE BY THE SUPERVISOR

This is to certify that the dissertation entitled **"Variation of Flow Property of Different Set of Formulas of Excipients Against Variable Ratio of Different Diluents"**, 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 **Mahjabin Haque**, **ID No. 2010-1-70-020** 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 **"Variation of Flow Property of Different Set of Formulas of Excipients Against Variable Ratio of Different Diluents"** is a genuine research work carried out by **Mahjabin Haque**, under the supervision of **Md. Anisur Rahman** (Senior Lecturer, Department of Pharmacy, East West University, Dhaka). I further certify that no part of the thesis has been submitted for any other degree and all the resources of the information in this connection are duly acknowledged.

Prof. Dr. Chowdhury Faiz Hossain

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Mahjabin Haque

Dedication

This Research Paper is Dedicated

To

My Beloved Parents

ABSTRACT

This work was proposed to determine flow properties of different set of some important pharmaceutical excipients that are most commonly used for the directly compressible tablets and to search for some equations which can predict the flow property of any set of excipients with different ratio of diluents. 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. Diluents were mixed with these prepared formulas in different specific and justified ratio. The prepared mixture in a constant weight (5g) was then examined for measuring flow property. The values of Carr's index, Hausner ratio and angle of repose were plotted against the percentage ratios of diluents. The study showed a linear relationship with different ratios of mixture and flow property measuring parameters. From these graphs the straightline equation 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 diluents and a specific set of other excipients were proposed that showed better flow property.

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Chapter One

INTRODUCTION

1.1 INTRODUCTION

The objective of the research project was to determine the flow properties of different pharmaceutical excipients individually and in combination as well. In this experiment, flow properties are measured by observing Carr's's index, Hausner ratio and angle of repose. These are the different reliable parameters of measuring the flow properties of substances.

In a formulation development, apart from active ingredients, inactive excipients play a major role. Pharmaceutical excipients are substances other than the pharmacologically active drug or prodrug which are included in the manufacturing process or are contained in a finished pharmaceutical product dosage form. So it is necessary to check the physicochemical properties of pharmaceutical excipients. For a definite pharmaceutical formulation, choosing the appropriate combination of excipients which can serve the required quality is essential. For this reason measurement of flow properties of powders is considered mandatory in any tablet or capsule formulation.

The purpose of this research project was to find out the variable flow properties of any set of excipients from plotting a standard curve of a particular combination of excipients. For accurate result, the experiments were done three times and all the guidelines were followed.

1.2 Powder flow property:

Powder flowability is the ability of a powder to flow in a desired manner in a specific piece of equipment. The flow property of powder plays an important role in dosage form manufacturing process. When limited amounts of drugs are available these can be evaluated simply by measurement of bulk density and angle of repose. These are extremely useful derived parameters to assess the impact of changes in drug powder properties as new batches become available.

Flow behavior is multi-dimensional and depends on many powder characteristics. In fact, flowability is not an inherent material property at all. Flowability is the result of a combination of material physical properties that affect flow, and the equipment used for handling, storing, or processing the material. The specific properties of a powder that affect its flow are known as flow properties. Bulk density, true density, permeability, cohesive strength, and wall friction are some of the examples of flow properties.

Powder flow is a key requirement for pharmaceutical manufacturing process. Tablets are often manufactured on a rotary multi-station tablet press by filling the tablet die with powders or granules based on volume. Thus, the flow of powder from the hopper into the dies often determines weight, hardness, and content uniformity of tablets. In case of capsules manufacturing, similar volume filling of powders or granules is widely used. Understanding of powder flow is also crucial during mixing, packaging, and transportation. And thus, it becomes essential to measure the flow properties of these materials prior to tableting or capsule filling (Freemantech, 2013).

1.2.1 Importance of Flow property studies of powder material:

1. In the pharmaceutical industry uniform flow of powders is one of the most important consolidations in solid dosage formulation. Improper feeding of powders from storage hoppers can lead to inconsistent product quality that ultimately causes economic and health impacts.
2. Different stages of manufacturing procedure such as blending, transfer, storage, compaction all depend on good powder flowability.
3. Designing and troubleshooting mass flow hoppers requires the measurement of powder flow.
4. Tableting operations require excipients with the desired flow, physical and mechanical properties.
5. Measurement of flow property is important phenomena as uniform flow of solid mixtures is one of the most important considerations in solid dosage formulation.

6. By observing flow property of pharmaceutical excipients some physical properties of desired pharmaceutical product such as weight uniformity, content uniformity, hardness, disintegration time can be maintained.
7. To design reliable devices for the handling of bulk solids, knowledge of the flow properties of these bulk solids is essential.

1.2.2 Factors influencing the flow property of powders:

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-

1. Particle size & 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.

2. Particle shape: Particle shape is of upmost importance in order to get required flow behavior. 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.

3. 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.

4. 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.

5. 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.

6. 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.

1.2.3 Parameters of measuring flow properties of powders:

The widespread use of powders in the pharmaceutical industry has generated a variety of methods for characterizing powder flow. It is a well known fact that the flow properties are multifaceted that's why the characterization of powder flow is complicated process. Here the processes of measuring powder flow are discussed which act promising to identify flow characteristics of powders.

The commonly used methods for testing powder flows that yields meaningful, practical, sensitive, reproducible and useful results are:

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

However, there are numerous variations of these methods, test methodology and operating scheme (Pharmacopeia, 2013).

1.2.3.1 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).

Figure 1.1: Angle of repose

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).

1.1 Table: Relation between flow properties and angle of repose

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

There are several different methods of determining the angle of repose namely,

- ✓ Tilting box method: This method is appropriate for fine-grained, non-cohesive materials, with individual particle size less than 10 mm. The material is placed within a box with a transparent side to observe the granular test material. It should initially be level and parallel to the base of the box. The box is slowly tilted at a rate of approximately 0.3 degrees/second. Tilting is stopped when the material begins to slide in bulk, and the angle of the tilt is measured.
- ✓ Fixed funnel method: The material is poured through a funnel to form a cone. The tip of the funnel should be held close to the growing cone and slowly raised as the pile grows, to minimize the impact of falling particles. Stop pouring the material when the pile reaches a predetermined height or the base a predetermined width. Rather than attempt to measure the angle of the resulting cone directly, divide the height by half the width of the base of the cone. The inverse tangent of this ratio is the angle of repose.
- ✓ Revolving cylinder method: The material is placed within a cylinder with at least one transparent face. The cylinder is rotated at a fixed speed and the observer watches the material moving within the rotating cylinder. The effect is similar to watching clothes tumble over one another in a slowly rotating clothes dryer. The granular material will assume a certain angle as it flows within the rotating cylinder. This method is recommended for

obtaining the dynamic angle of repose, and may vary from the static angle of repose measured by other methods. When describing the angle of repose for a substance, always specify the method used.

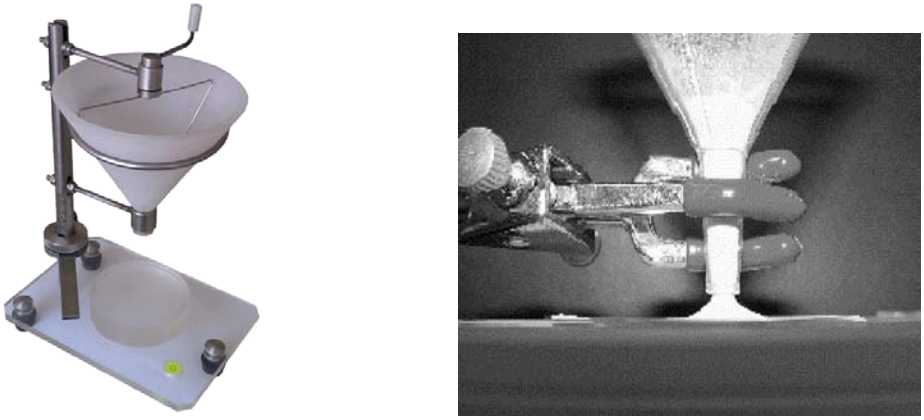

Figure 1.2: [Left to right] *A set up of funnel with stand and measuring angle of repose*

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

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

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

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).

1.2.3.2 Compressibility index and Hausner ratio

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.

1.2.3.2.1 Compressibility index:

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.

The Carr's index is 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,

V_o = Bulk volume

V_f = Tapped volume

The Carr's index is frequently used in pharmaceutics as an indication of the flowability of a powder. In a free-flowing powder, the bulk density and tapped density would be close in value; therefore, the Carr's index would be small. On the other hand, in a poor-flowing powder where there are greater interparticle interactions, the difference between the bulk and tapped density observed would be greater, therefore, the Carr's index would be bigger. A Carr's index greater than 25 is considered to be an indication of poor flowability, and below 15, of good flowability. So the smaller the Carr's index the better the flow properties.

The compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of materials. These properties can influence the Carr's index.

1.2.3.2.2 Hausner 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.

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

The compressibility index and Hausner ratio are not intrinsic properties of the powder. They depend on the methodology used.

1.2.3.2.3 The inter-relation between the Carr's index and Hausner ratio:

The Hausner ratio (H) is related to the Carr's index (C), by the formula:

H=100/ (100-C)

1.2 Table: Relation between flow properties with Compressibility index (Carr's index) and Hausner ratio

Table 2.9.36.-2. – *Scale of flowability*[2]

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

The compressibility index and Hausner ratio are determined by measuring both the bulk volume (unsettled apparent volume) and the tapped volume of the powder (after tapping the material until no further volume changes occur).

1.2.3.3 Bulk density and Tapped density

1.2.3.3.1 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.

1.2.3.3.2 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).

By measuring both the untapped volume and the tapped volume the following can be determined.

- Bulk volume = volume of powder + volume of intra particle space + voids
- True volume = the volume of powder itself
- Bulk density = mass/untapped volume
- Tapped density = mass/tapped volume (Slideshare, 2012).

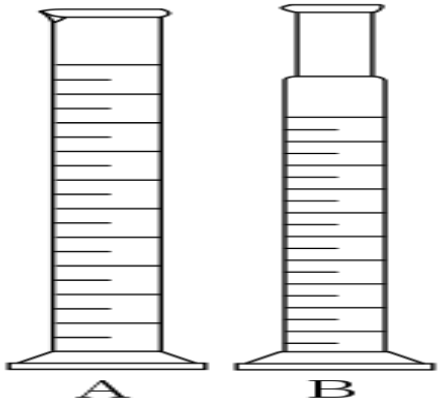

Figure 1.3: Bulk volume measurement without tapping (A) and Tapped volume measurement after tapping (B)

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.

1.2.3.3.3 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

1.3 Pharmaceutical excipients used in directly compressible dosage form

Pharmaceutical excipient is 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 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. An excipient is an inactive substance formulated alongside the active ingredient of a medication, for the purpose of bulking-up formulations that contain potent active ingredients (Pharmacopeia, 2013).

1.3.1 Classification of pharmaceutical excipients:

The manufacturing of a tablet includes compressing a drug with several excipients. Different pharmaceutical excipients were chosen that are used in different solid dosage formulations. The pharmaceutical excipients are classified into various classes according to their application and uses. Most often a pharmaceutical excipient may serve a number of purposes.

1.3.1.1 List of pharmaceutical excipients of various classes:

1.3.1.1.1 Diluents:

Diluents are an inert substance that lacks pharmacologic activity but is pharmaceutically desirable to increase the bulk of potent drug substances. They are also synonymously known as fillers. It is a thinning agent made up of a mixture of organic compounds containing the lighter hydrocarbons. Diluents simply change the concentration of the chemicals within the product but not the physical form of it. Usually the range of diluents varies from 5-80% (Drugs.com, 2013).

The range of tablet diluents may vary from 5-80%. Diluents are often added to tablet formulations to provide better tablet properties such as:

- ✓ To improve cohesion
- ✓ To allow direct compression manufacturing
- ✓ To enhance flow
- ✓ To adjust weight of tablet as per die capacity

Diluents/filler for tablet must meet some criteria. They are as follows:

- ➢ Diluents should not react with the drug substance and moreover it should not have any effect on the functions of other excipients
- ➢ It should not have any physiological or pharmacological activity of its own
- ➢ It should have consistent physical and chemical characteristics

- It should neither promote nor contribute to segregation of the granulation or powder blend to which they are added
- It should be able to be milled (size reduced) if necessary in order to match the particle size distribution of the active pharmaceutical ingredient
- It should neither support microbiological growth in the dosage form nor contribute to any microbiological load
- It should neither adversely affect the dissolution of the product nor interfere with the bioavailability of active pharmaceutical ingredient
- It should preferably be colorless or nearly so.

Tablet diluents or fillers can be divided into three categories:

i) Organic materials - Carbohydrate and modified carbohydrates:

· Lactose : a-lactose monohydrate, spray dried lactose and anhydrous lactose

· Starch and Pregelatinized Starch

· Sucrose, Manitol, Sorbitol

· Cellulose : Powdered Cellulose, Microcrystalline Cellulose

ii) Inorganic materials

· Calcium phosphates, Anhydrous Dibasic Calcium Phosphate, Dibasic Calcium Phosphate, Tribasic Calcium Phosphate

iii) Co-processed Diluents (Vinensia, 2013).

1.3.1.1.2 Disintegrant:

A disintegrant is an excipient which is added to a tablet or capsule blend to aid in the breakup of the compacted mass when it is put into a fluid environment. This is especially important for immediate release products where rapid release of drug substance is required. A disintegrant can be added to a powder blend for direct compression or

encapsulation. It can also be used with products that are wet granulated**.** While there are some tablet fillers (e.g., starch and microcrystalline cellulose) which aid in disintegration, there are more effective agents referred to as superdisintegrants. They ensure that when the tablet is in contact with water, it rapidly breaks down into smaller fragments, facilitating dissolution.

Some commonly used disintegrants are as follows: Polyvinylpyrrolidone (PVP), sodium carboxymethyl cellulose, Sodium Starch Glycolate (Pformulate, 2000).

1.3.1.1.3 Lubricants or glidants:

Pharmaceutical lubricants and glidants are designed to promote smooth, effortless tablet ejection during manufacturing. The flow of the tablet powder blend is improved by the lubricant reducing interparticle friction.

Some commonly used lubricants are as follows:

Lubricants can be hydrophobic, such as magnesium stearate, or hydrophilic, such as boric acid or sodium lauryl sulfate. Other common glidants and lubricants include mineral oils, talcs, and sodium stearyl fumarate, calcium stearate, stearic acid.

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

1.3.1.1.4 Binders:

Binders are substances that ensure the mechanical strength of a tablet after it is compressed. In the pharmaceutical application, a tablet binder can be used for the purposes of direct compression or wet granulation. A binder may be a dry powder, paste, or made into a solution as a solvent.

Binders act as an adhesive to 'bind together' powders, granules and tablets to result in the necessary mechanical strength. Binders are added to tablet formulations to add cohesiveness to powders thereby providing the necessary bonding to form granules which under compaction form a compact mass as tablet. In other words, binders are essential to achieve the "hardness" of the tablet.

Tablet binders are used in the formulation of solid oral dosage forms to hold the active pharmaceutical ingredient and inactive ingredients together in a cohesive mix. Binder products are usually differentiated based on the manufacturing process to be used.

Binders are usually selected on basis of previous experience, particular product needs, literature or vendor data or the preference of individual scientists or manufacturing unit. The primary criterion when choosing a binder is its compatibility with other tablet components (Drugtopics, 2008).

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).

1.3.1.1.5 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.

1.4 Excipients used in the experiment:

1.4.1 Sodium lauryl sulfate

Sodium lauryl sulfate is used as a lubricant to eliminate friction during tablet compression and drawing out the mold. In tablet formulation Sodium lauryl sulfate act as lubricant in a range of 1-5%. Sodium lauryl sulphate increased absorption of water by starch or had a variable effect on water penetration in tablets. It is also a surfactant which is recommended to decrease the hydrophobicity of the drugs because the more hydrophobic the tablet the greater the disintegration time.

1.4.2 Starch

Starch is one of the earliest known binding agents to be used in tablet manufacturing process. It is a white powder without any odor or taste. Native starches are available from a wide variety of plant sources such as corn, potato and wheat. However, these varieties tend to be highly viscous, to agglomerate, and have poor flow properties, making their handling difficult during the tablet manufacturing process. Newer varieties such as pregelatinized starch help to overcome these drawbacks because they are pre-cooked and partly hydrolyzed during the production stage. Such varieties lend themselves well to wet

granulation as well as direct compression methods of tablet manufacture. Besides, it is directly compressible diluents. It possesses good binding properties and disintegrant activity.

1.4.3 Microcrystalline Cellulose

MCC is useful in the preparation of tablets prepared by direct compression as well as wet granulation methods. Plant fibers contain alpha cellulose which can be chemically modified by controlled hydrolysis. This yields a partially depolymerized form of cellulose called microcrystalline cellulose (MCC). Generally, this product has a polymerization degree less than 400. Unlike other traditional binders that slow down the process of tablet disintegration, MCC acts as a binding and disintegrating agent. Tablets containing MCC should not be exposed to high humidity conditions, which tend to soften the tablets.

1.4.4 Povidone

It is chemically known as polyvinyl pyrollidone. Povidone is a common binder generally used at a concentration of 5 percent. It is a polymer available in different grades depending on the molecular weight. It is soluble in water and other solvents generally used in pharmaceutical manufacturing. It acts as a binding agent for wet granulation and direct compression methods. Some grades of povidone are also useful in the preparation of sustained release tablets.

1.4.5 Magnesium Stearate

Magnesium stearate is the most commonly used and most effective of all lubricants. It is also the most likely to cause compression & dissolution problems. Concentration, grade and mixing parameters must be carefully controlled. These stearates are alkaline in reaction. It is incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing

aspirin, some vitamins, and most alkaloidal salts. Magnesium stearate has good glidant and anti-adherent properties.

1.4.6 Talc

Talc is not particularly effective on its own as a tablet lubricant or glidant but very effective with lubricants in the role of an anti-adherent in that it effectively prevents sticking to surfaces. When using talc, it should always be blended into the formulation first followed by the lubricant (i.e. magnesium stearate). The usable concentration of talc is in a range of 1-10%. Talc incompatible with quaternary ammonium compounds. It is not soluble in water.

1.4.7 Calcium phosphates

They are granular insoluble materials. They are widely used both as wet granulation and direct compression diluents in tablet formulation. Bulk density of calcium phosphates is higher than that of organic fillers. They are directly compressible and are characterized by brittle fracture on compression during tableting process. Hard tablets are produced when calcium phosphates are used as diluents. They exhibit good flow properties. They are non hygroscopic and inexpensive.

1.4.8 Lactose

Several grades are available such as Lactose monohydrate, spray dried lactose and anhydrous lactose is widely used as diluents. It is directly compressible diluents. It exhibits free flowing characteristics. It is more prone to darkening in the presence of excess moisture, amines and other compounds due to the presence of a furaldehyde. It has no reaction with most active ingredients. Lactose on storage tends to lose moisture.

1.4.9 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).

1.4.10 Boric acid

Boric acid additive lubricants significantly outperformed all of the other lubricants with respect to frictional and wear performance. Boric acid owes its lubricious properties to its unique natural structure. Boric acid is a weak acid of boron often used as an antiseptic which exists in the form of colorless crystals or a white powder that dissolves in water.

1.4.11 Hydroxypropylmethylcellulose (HPMC)

Hydroxypropyl methylcellulose (HPMC) is a semisynthetic, inert substance used as a lubricant, as well as an excipient and controlled-delivery component in oral medicaments, found in a variety of commercial products.

HPMC is a white to light yellow powder or granular product. HPMC, a multipurpose additive for pharmaceutical, can be functioned as thickener, dispersant, emulsifier, film forming agent, etc. It is used in tablets for dressing and binding to improve solubility of the drugs. It functions as controlled release agent to delay the release of a medicinal compound into the digestive tract. It is also used as a binder and as a component of tablet coatings (Alibaba, 2013).

Chapter Two

LITERATURE REVIEW

2.1 LITERATURE REVIEW

In 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 indicates that these lubricants have 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 these lubricants. If the concentration of lubricant gets lower, the antistatic effectiveness is decreased.

The next 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 have been chosen since they possess subjective or indirect methods like angle of repose measurement. These are fumed silicon dioxide, magnesium stearate, starch and talc in combination with other selected materials. Researchers observed that some widely used glidants may decrease the flow rate. The results they found that is the flow of glidants cannot 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.

In the year 1979, Bolhuis, Lerk, and Moes (Bolhuis et al., 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^{o}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.

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.

Then after many more 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) evaluated the powder characteristics and tableting properties of Ludipress which is a combination of povidone and crosspovidone. The scientists made a comparison with other binders.

The study was to find out the flowability, bulk density, tapped density, Hausner ratio, angle of repose and particle size distribution in which morphological study were evaluated primarily. It has been stated that several samples of ludipress showed a good uniformity and flow characteristics than other excipients. The data was found by assessing the tableting parameters like crushing strength, friability and disintegration time.

The effect of eleven pharmaceutical excipients with Avicel PHI02 SCG was investigated by two scientists, Flemming and Mielck (Flemming and Mielck, 1995) in the next 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 has been performed 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.

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 indicates that surface energy differences

detected by IGC can be related to important secondary processing properties such as powder flow.

In the twentieth century, Taylor and his coworkers (Taylor et al., 2000) 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 and further studies are necessary for better assessment of these approaches.

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 accounts for more than 80% of the administered dosage form. Here the study has given emphasis on the expected result in accordance with their functionality. They want 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.

In 2001, Hancock and his research fellow (Hancock et al., 2001) evaluated two recently developed matrix forming polymers like cross-linked high-amylose starch and poly

acrylic 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 and his fellow researchers (Gabaude et al., 2001) compared between four techniques. For the measurement of powder flow properties, two methods are considered that are packing and rearrangement under pressure methods or shear cell measurement methods. The reduction of the powder bed volume under low pressures is evaluated by two compressibility methods such as uniaxial press and volumenometer. Flow functions are 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 is actually well interconnected with shear cell measurements and it is more precise than classical flowability tests recommended by the European Pharmacopoeia. The research concluded with the statement that this method is easy to use with a quite accurate estimation of powder flow properties of new drug substances and consumes a small amount of powders less than 1g.

Mullarney and his research team (Mullarney et al., 2003) studied on the physical flow and mechanical properties of common pharmaceutical excipients (sweeteners) that are frequently used in solid dosage form formulation. Here stated that the selected sweeteners have different particle size, shape and true density. Their powder flow characteristics, mechanical properties and cohesivity test were performed. They found that some sweeteners such as sucrose and acesulfame potassium showed excellent flowability,

whereas saccharin sodium and aspartame were proven poor flowable substances. So, it can be stated that, a careful selection of suitable sweetener is mandatory to obtain desirable flowability.

The effect of pharmaceutical excipients on properties affecting tablet production was evaluated by Nagel and Peck (Nagel and Peck, 2003). They discovered that pharmaceutical excipients have great impact on the tableting properties. They also took an attempt to establish the use of theophylline anhydrous in formulation so that it can be easily tableted. They examined Carr's's index to measure flowability. Besides, the active ingredient, theophylline anhydrous, the formulation contains hydrous lactose and dicalcium phosphate as diluents, PVP as binder, fumed silica as flow promoter and the powder flow for each component was evaluated effectively.

In the year 2004 Lindberg and his research team (Lindberg et al., 2004) 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.

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 refers 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.

The following year Bhattachar and his fellow scientists (Bhattachar et al., 2004) introduced the statement that in the development of dosage form, the flow properties of pharmaceutical powders in solid oral dosage forms is a fundamental phenomena. In this case, the vibratory feeder method was considered as the flow measurement technique to measure flow properties of common pharmaceutical powders in solid oral dosage forms. In these experiment, seventeen various powders were evaluated with the instrument to measure the flow properties and the result was included in the powder flow index (PFI). On the other hand, the powder flow was evaluated with another commonly used alalanche instrument and similarly the data was included in MTA as mean time. The results obtained from the two different instrumental method having different algorithms, were compared with nonparametric statistical assessment of the data and proved as a reliable document. Afterwards, vibratory feeder method was recommended for measuring powder flow.

In the year 2005, Kachrimanis, Petrides, and Malamataris (Kachrimanis et al., 2005) 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.

In the year 2007, Jacob and his research fellows (Jacob et al., 2007) 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 have 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 have optimized powder and compressibility characteristics with fast disintegrating property. They concluded that higher rate of powder flow can indirectly influence the rate of disintegration.

Hou and Sun (Hou and Sun, 2008) investigated the effects of particle size, morphology, density on flow properties using a ring shear tester under the parameter of flow function. The study showed that smaller particles exhibit poor powder flow properties. Reduction of particle size had an effect on flow properties. If the powder has different density but similar particle size, shape and surface area, they have similar flow properties. In contrast, better flow property achieved by higher particle density.

After two years, the one and only scientist Sun (Sun, 2010) discovered that in tablet manufacturing process an inadequate powder flow leads to a great problem. Besides, a minimum knowledge of flow properties for efficient pharmaceutical tablet development is required for successful tableting result. The finding was achieved in order to discover 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. This data also can 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.

The same year Sarraguca and his co-workers (Sarraguca et al., 2010) determined the flow properties of pharmaceutical powders by near infrared spectroscopy. They illustrated that physical properties of pharmaceutical powders are of topmost importance in the pharmaceutical industry. They examined the critical significance of flow properties on processes like blending, tablet compression, capsule filling and transportation using angle of repose, Carr's's index and Hausner ratio. They used near infrared spectroscopy which is a fast and low-cost analytical technique to determine the parameters of flow properties of pharmaceutical powders based on active ingredient paracetamol. The spectra were recorded on a Fourier-transform near infrared spectrometer in which the parameters were the angle of repose, true and tapped density. The comparison was made between near infrared based properties and reference methods results. The result showed that the physical properties affect the flowability of pharmaceutical powders.

Chattoraj, Shi and Sun (Chattoraj et al., 2011) demonstrated that poor flow properties hinder the easy handling of powders during industrial-scale processing. In their experiment, they showed that powder flow can 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 has been made with specified preparation at vigorous mixtures. The flow properties of nanocoated Avicel PH105 are comparable to those of Avicel PH102, which exhibits 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 includes mean residence time, and axial dispersion coefficient. The function of input parameters is 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.

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.	Carboxymethyl Cellulose	MERK, Germany
2.	Calcium Phosphate	MERK, Germany
3.	Lactose	MERK, Germany
4.	Magnesium Stearate	MERK, Germany
5.	Polyvinyl pyrrolidine	MERK, Germany
6.	Sodium Lauryl Sulphate	MERK, Germany
7.	Starch	MERK, Germany
8.	Talc	MERK, Germany

3.1.3 Equipments and Instruments:

Table 3.2: List of instruments through this research work

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

3.1.4 Images of Instruments:

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

Figure 3.1: Mixture Machine

Figure 3.2: Electronic Balance

3.1.5 Apparatus:

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

Table 3.3: List of apparatus used throughout this research work

Serial No.	Apparatus
1.	Beaker
2.	Test tubes
3.	Aluminum Foil Paper
4.	Cling Wrap (Transparent Plastic Paper)
5.	Mortar & Pastels
6.	Spatula
7..	Funnel
8.	Measuring Cylinder
9.	Conical Flask
10.	White Paper
11.	Desiccant
12.	Black Marker
13.	Scale

3.2 METHODS

3.2.1 Preparation of various set of formulas:

Several formulas of a combination of excipients which includes lubricants, disintegrants, binders and antiadherents were made. In some set of formulas all these ingredients were chosen whereas some set of formulas may lack any of them. Specific substance from a specified class of excipient was chosen randomly and weighed in the electronic balance in a calculated amount. In these ways various formulas were made of 10 to 20g based on the required quantity to test which are denoted by F1, F2, F3 and so on. The prepared formulas were taken in a beaker and mixed well by a mixer machine.

3.2.2 Preparation of mixture of formula and constant excipient (Diluents):

After that, a 5g sample was made through calculating the required amount of the formula with the selected diluents. Diluents were mixed with the prepared formulas in a specified ratio and again the mixture was mixed in the individual test tubes by hand shaking. In this way for a specific set of excipient and a selected diluent, four different mixtures of 5g each were arranged and settled in four test tubes. The test tubes were labeled properly. These test tubes were then ready for measuring individual flow properties by observing its bulk volume, tapped volume which ultimately yields Carr's index and Hausner ratio and angle of repose as well.

3.2.3 Flow property measurement:

3.2.3.1 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.

3.2.3.2 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.

3.2.3.3 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,

V_o = Bulk volume

V_f = Tapped volume

3.2.3.4 Measurement of Angle of repose:

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

3.2.3.4.1 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.

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

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

3.2.4 Preparation of Formulas

3.2.4.1 Preparation of Formula 1 (F1):

By choosing different excipients from different classes except diluents, formula 1 (F1) was prepared. Here the selected excipient 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)-10g

Ingredients Name	Purpose of Use	Percentage Quantity	Amount in 10g
Talc	Lubricant	40%	4
PVP	Disintegrant	20%	2
Magnesium stearate	Antiadherent	12%	1.2
PEG	Binder	28%	2.8
		Total = 100%	Total = 10g

After preparing 10g of F1, specific diluent was mixed with it in different fixed and justified ratio. For this formula, lactose was used. The required amount of both lactose and F1 was calculated for preparing each 5g of mixture in four different ratios. A total of four sets of sample mixture of 5g were set up for further procedure that is the determination of flow property.

3.5 Table: The amount of lactose and F1 in different ratio (Set-1) in 5g

Ratio	lactose : F1	Amount of lactose : F1 (in g)
1	75% : 25%	3.75 : 1.25
2	65% : 35%	3.25 : 1.75
3	55% : 45%	2.75 : 2.25
4	45% : 55%	2.25 : 2.75

3.2.4.2 Preparation of Formula 2 (F2):

By choosing different excipients from different classes except diluents, formula 2 (F2) was prepared. Here the selected excipient 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)-20g

Ingredients Name	Purpose of Use	Percentage Quantity	Amount in 20g
HPMC	Disintegrant	33.33%	6.67
Starch	Binder	50%	10
Sodium lauryl sulfate	Lubricant	6.67%	1.33
Magnesium stearate	Antiadherent	10%	2
		Total = 100%	Total = 20g

After preparing 20g of F2, specific diluents were mixed with it in different fixed and justified ratio. For this formula, calcium phosphate was used. The required amount of both calcium phosphate and F2 was calculated for preparing each 5g of mixture in four different ratios.

A total of four sets of sample mixture of 5g were set up for further procedure that is the determination of flow property.

3.7 Table: The amount of calcium phosphate and F2 in different ratio (Set-2) in 5g

Ratio	Calcium phosphate : F2	Amount of lactose : F2 (in g)
1	55% : 45%	2.75 : 2.25
2	65% : 35%	3.25 : 1.75
3	75% : 25%	3.75 : 1.25
4	85% : 15%	4.25 : 0.75

3.2.4.3 Preparation of Formula 3 (F3):

By choosing different excipients from different classes except diluents, formula 3 (F3) was prepared. Here the selected excipient 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)-20g

Ingredients Name	Purpose of Use	Percentage Quantity	Amount in 20g
PVP	Disintegrant	25%	5
Magnesium stearate	Antiadherent	15%	3
CMC	Binder	30%	6
Boric acid	Lubricant	30%	6
			Total = 20g

After preparing 20g of F3, specific diluents was mixed with it in different fixed and justified ratio. For this formula, starch was used. The required amount of both starch and F3 was calculated for preparing each 5g of mixture in four different ratios. A total of four sets of sample mixture of 5g were set up for further procedure that is the determination of flow property.

3.9 Table: The amount of starch and F3 in different ratio (Set-3a) in 5g

Ratio	Starch: F3	Amount of starch: F3 (in g)
1	40% : 60%	2 : 3
2	50% : 50%	2.5 : 2.5
3	60% : 40%	3 : 2
4	70% : 30%	3.5 : 1.5

After that, using the same formula (F3) a different mixture was prepared in which lactose was used as diluents. The same procedure was repeated for this experiment also.

3.10 Table: The amount of lactose and F3 in different ratio (Set-3b) in 5g

Ratio	Lactose : F3	Amount of lactose : F3 (in g)
1	45% : 55%	2.25 : 2.75
2	55% : 45%	2.75 : 2.25
3	65% : 35%	3.25 : 1.75
4	75% : 25%	3.75 : 1.25

3.2.4.4 Preparation of Formula 4 (F4):

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

3.11 Table: The following amounts of excipients (given with their use) were taken for the preparation of Formula 4 (F4)-30g

Ingredients	Purpose of Use	Percentage Quantity	Amount in 30g
Talc	Lubricant	15%	4.5
Starch	Disintegrant	20%	6
Zinc stearate	Antiadherent	5%	1.5
Lactose	Binder	35%	10.5
PVP	Granulating agent	25%	7.5
			Total = 30g

After preparing 30g of F4, specific diluents was mixed with it in different fixed and justified ratio. For this formula, was used. The required amount of both calcium phosphate and F4 was calculated for preparing each 5g of mixture in four different ratios. A total of four sets of sample mixture of 5g were set up for further procedure that is the determination of flow property.

3.12 Table: The amount of calcium phosphate and F4 in different ratio (Set-4a)in 5g

Ratio	Calcium phosphate : F4	Amount of calcium phosphate: F4 (in g)
1	35% : 65%	1.75 : 3.35
2	45% : 55%	2.25 : 2.75
3	55% : 45%	2.75 : 2.25
4	65% : 35%	3.25 : 1.75

After that, using the same formula (F4) a different mixture was prepared in which starch was used as diluents. The same procedure was repeated for this experiment also.

3.13 Table: The amount of starch and F4 in different ratio (4b)in 5g

Ratio	Starch: F4	Amount of starch: F4 (in g)
1	30% : 70%	1.5 : 3.5
2	40% : 60%	2 : 3
3	50% : 50%	2.5 : 2.5
4	60% : 40%	3 : 2

3.2.4.5 Preparation of Formula 5 (F5):

By choosing different excipients from different classes except diluents, formula 5 (F5) was prepared. Here the selected excipient from a particular class will serve the properties of itself in that range of amount not the others.

3.14 Table: The following amounts of excipients (given with their use) were taken for the preparation of Formula 5 (F5)-20g

Ingredients	Purpose of Use	Percentage Quantity	Amount in 20g
HPMC	Binder	50%	10
Sodium lauryl sulfate	Lubricant	10%	2
Zinc stearate	Antiadherent	5%	1
Starch	Disintegrant	25%	5
PVP	Lubricant	10%	2
		Total = 100%	Total = 20g

After preparing 20g of F5, specific diluents was mixed with it in different fixed and justified ratio. For this formula, was used. The required amount of both lactose and F5 was calculated for preparing each 5g of mixture in four different ratios. A total of four

sets of sample mixture of 5g were set up for further procedure that is the determination of flow property.

3.15 Table: The amount of lactose and F5 in different ratio (Set-5a) in 5g

Ratio	Lactose : F5	Amount of Lactose : F5 (in g)
1	50% : 50%	2.5 : 2.5
2	60% : 40%	3 : 2
3	70% : 30%	3.5 : 1.5
4	80% : 20%	4 : 1

After that, using the same formula (F5) a different mixture was prepared in which talc was used as diluents. The same procedure was repeated for this experiment also.

3.16 Table: The amount of talc and F5 in different ratio (Set-5b) in 5g

Ratio	Talc: F5	Amount of talc : F5 (in g)
1	25% : 75%	1.25 : 3.75
2	35% : 65%	1.75 : 3.35
3	45% : 55%	2.25 : 2.75
4	55% : 45%	2.75 : 2.25

Chapter Four

RESULTS

4.1 RESULTS

4.1.1 Calculation of individual excipients flow properties:

The flow property of individual excipients was 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 three times and the average value was taken. The observed value is given below:

4.1 Table: Calculation of individual excipients Carr's index and Hausner ratio

Ingredients	Bulk	Avg Bulk	Tapped	Avg Tapped	Hausner Ratio	Carr's's Index
Sodium Iauryl Sulfate	17	16.8	14.5	14.1	1.191	16.071
	16.5		14			
	17		14			
Magnesium Sulfate	52	52.5	40.5	40.1	1.309	23.619
	52.5		40			
	53		40			
Sucrose	4	4.1	3	3.1	1.322	24.39
	4.5		3.5			
	4		3			
Lactose	5.5	5.8	5	5	1.16	13.793
	6		5			
	6		5			
Talc	5	4.8	3	3	1.6	37.5
	5		3			
	4.5		3			
PEG	5	5	4	4	1.25	20
	5		4			
	5		4			

Ingredients	Bulk	Avg Bulk	Tapped	Avg Tapped	Hausner Ratio	Carr's's Index
Boric Acid	5	4.7	3.5	3.25	1.45	30.851
	4.7		3.25			
	4.5		3			
Starch	8	8.5	5	5	1.7	41.176
	9		5			
	8.5		5			
CMC	7	7.1	4	4	1.775	43.662
	7.5		4			
	7		4			
HPMC	10	9.8	7.5	7.25	1.36	26.02
	9.5		7.25			
	10		7			
PVP	8	8.1	6	6.1	1.328	24.691
	8.5		6.5			
	8		6			

For calculating angle of repose, their individual cone height and radius were measured three times and the average value was taken. The observed value is given below:

4.2 Table: Calculation of individual excipients angle of repose

Ingredients	Height (h)	Diameter (2r)	Radius(r)	Angle of Repose
Sodium Iauryl Sulfate	2.8	6	3	43.025
Magnesium Sulfate	2	5.2	2.6	37.568

Ingredients	Height (h)	Diameter (2r)	Radius(r)	Angle of Repose
Sucrose	1.1	4.2	2.1	27.645
Lactose	1.04	4	2	19.33
Talc	1.9	4	2	43.531
PEG	1	4.9	2.45	22.203
Boric Acid	1.6	3.9	1.95	39.369
Starch	2.6	5	2.5	46.123
CMC	1.7	4	2	40.364
HPMC	2.3	4.7	2.35	44.383
PVP	1.7	5.1	2.55	33.69

4.1.2 Calculation of flow property of the prepared mixture ratio of diluents and formulas:

4.1.2.1 For set 1:

The Carr's index and Hausner ratio of set-1 was calculated by their bulk volumes and tapped volumes which were measured three times and the average value was taken. The observed value is given below:

4.3 Table: Calculation of Carr's index and Hausner ratio for set-1

lactose : F1	Bulk	Avg Bulk	Tapped	Avg Tapped	Carr's's Index	Hausner Ratio
75:25	9.5 9 8.5	9	7.5 7.2 6.9	7.2	20	1.25
65:35	9.5 9 8.5	9	7 7 7	7	22.22	1.28
55:45	9.5 9 8.5	9	7 6.6 6.2	6.6	26.66	1.36
45:55	10 9.5 9	9.5	7.3 6.9 6.5	6.9	27.315	1.37

By plotting percentage ratio of lactose 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 can be achieved.

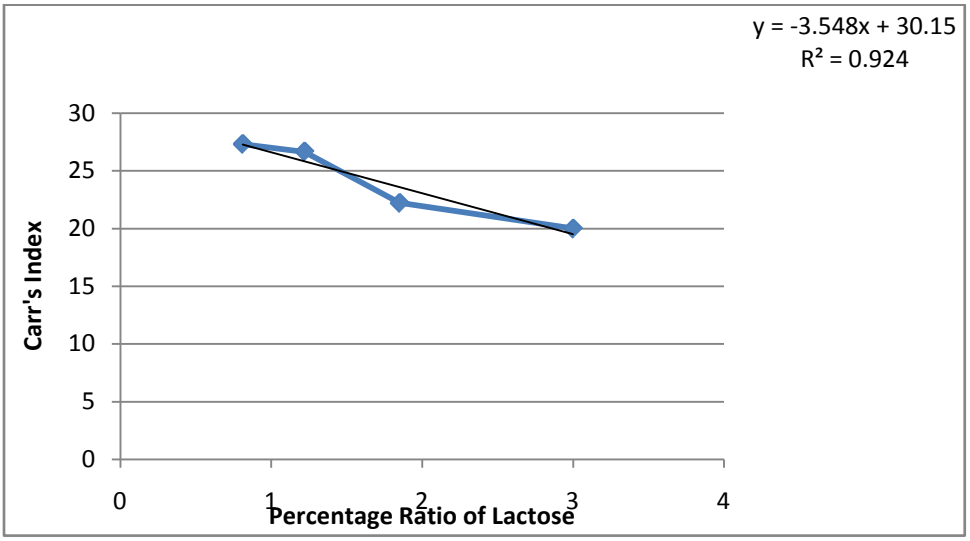

Figure 4.1: A percentage ratio of lactose versus Carr's index graph

By plotting percentage ratio of lactose 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 can be achieved.

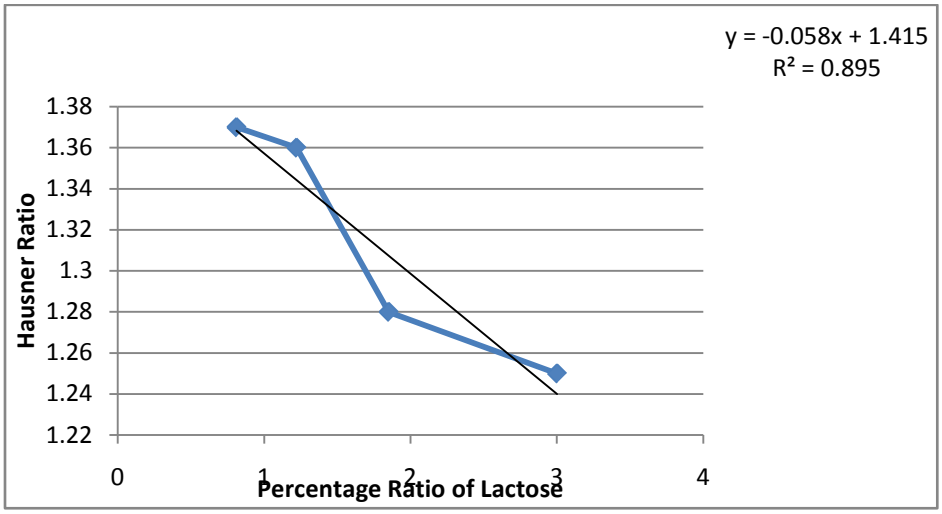

Figure 4.2: A percentage ratio of lactose versus Hausner ratio graph

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

4.4 Table: Calculation of Angle of repose for set-1

Lactose : F1	Height (h)	Avg Height (h)	Diameter (2r)	Avg Diameter (2r)	Radius (r)	Angle of Repose
75:25	2 1.7 1.4	1.7	5.2 4.7 4.2	4.7	2.35	36.155
65:35	2 1.6 1.2	1.6	5 4.5 4	4.5	2.25	36.847
55:45	2.5 2 1.5	2	5.5 5 4.5	5	2.50	38.659
45:55	3 2.4 1.8	2.4	6 5.7 5.4	5.7	2.85	40.100

By plotting percentage ratio of lactose 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 can be achieved.

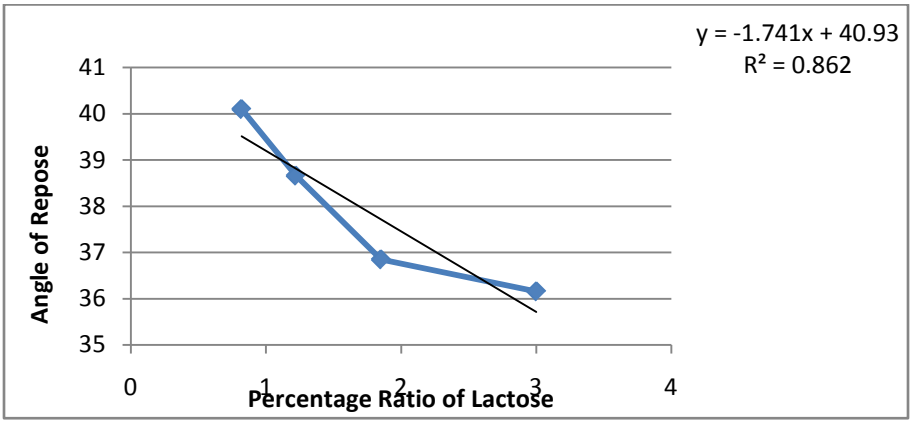

Figure 4.3: A percentage ratio of lactose versus angle of repose graph

4.1.2.2 For set 2:

The Carr's index and Hausner ratio of set-2 was calculated by their bulk volume and tapped volumes which were measured three times and the average value was taken. The observed value is given below:

4.5 Table: Calculation of Carr's index and Hausner ratio for set-2

Calcium phosphate : F2	Bulk	Avg Bulk	Tapped	Avg Tapped	Carr's's Index	Hausner Ratio
55:45	14 13.5 13	13.5	10 9.5 9	9.5	29.629	1.421
65:35	11.5 11 10.5	11	8.5 8 7.5	8	27.27	1.375
75:25	12 11.5 11	11.5	8.5 8 7.5	8	30.434	1.4375
85:15	12.5 12 11.5	12	8 7.5 7	7.5	37.5	1.6

By plotting percentage ratio of calcium phosphate 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 can be achieved.

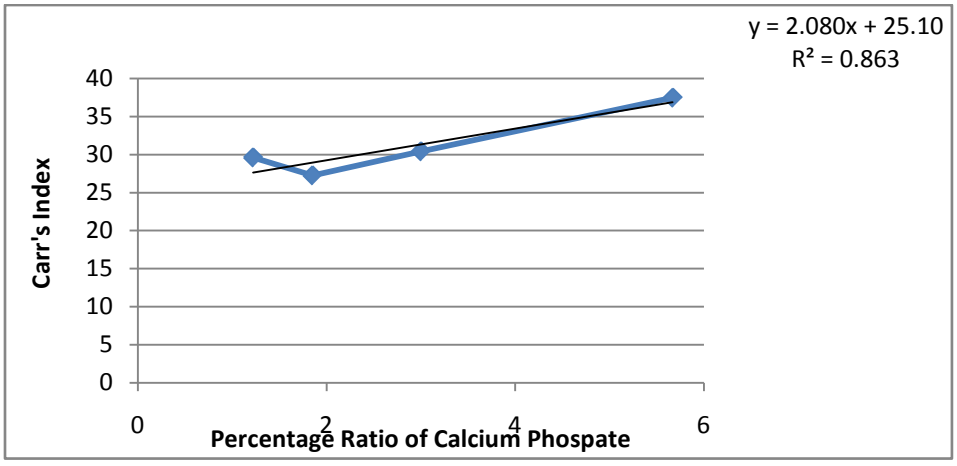

Figure 4.4: A percentage ratio of calcium phosphate versus Carr's index graph

By plotting percentage ratio of calcium phosphate 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 can be achieved.

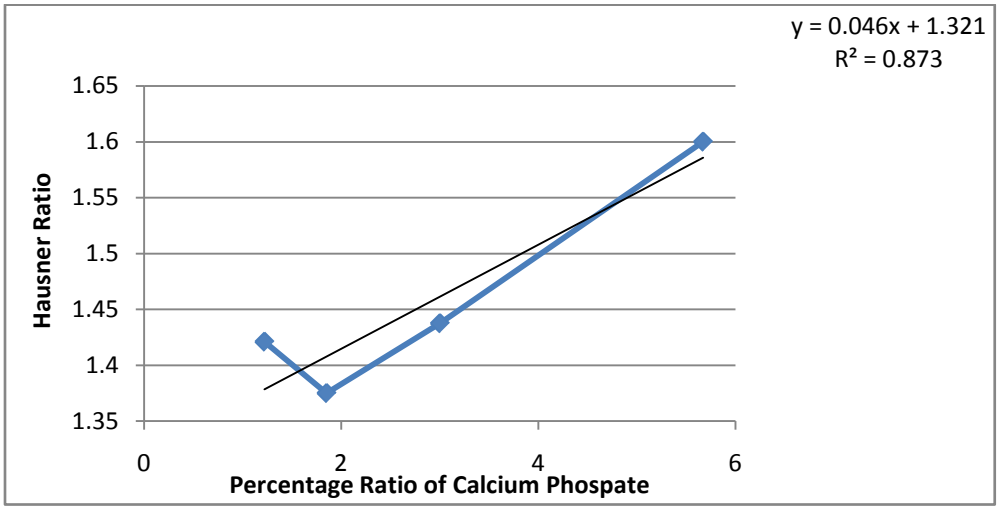

Figure 4.5: A percentage ratio of calcium phosphate versus Hausner ratio graph

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

4.6 Table: Calculation of Angle of repose for set-2

Calcium phosphate : F2	Height (h)	Avg Height (h)	Diameter (2r)	Avg Diameter (2r)	Radius (r)	Angle of Repose
55:45	3 2.4 1.8	2.4	6.5 6 5.5	6	3	38.659
65:35	2.8 2.3 1.8	2.3	5.5 5 4.5	5	2.5	42.614
75:25	3 2.3 1.6	2.3	5.2 4.7 4.2	4.7	2.35	44.383
85:15	2.7 2.3 1.9	2.3	5 4.4 3.8	4.4	2.2	46.289

By plotting percentage ratio of calcium phosphate 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 can be achieved.

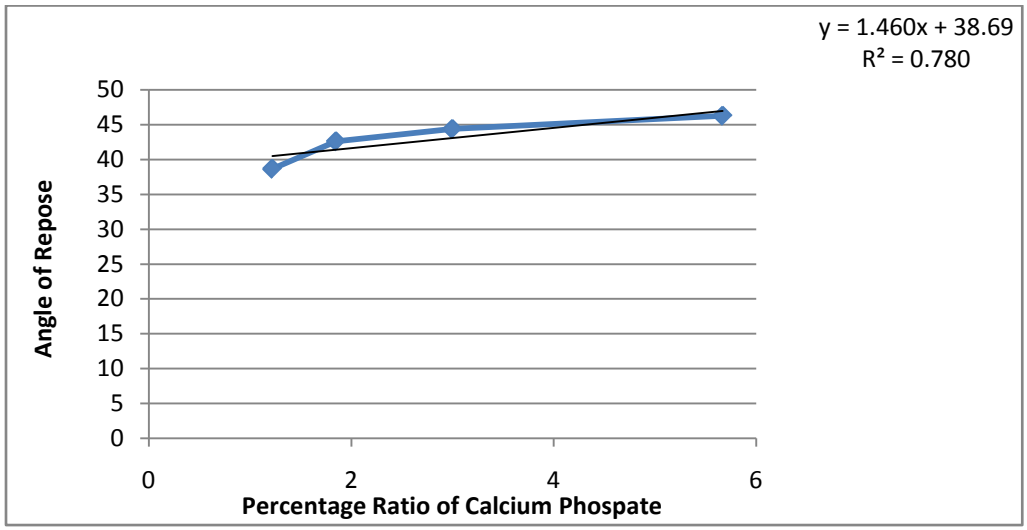

Figure 4.6: A percentage ratio of calcium phosphate versus angle of repose graph

4.1.2.3 For set 3a:

The Carr's index and Hausner ratio of set-3a was calculated by their bulk volume and tapped volume which was measured three times and the average value was taken. The observed value is given below:

4.7 Table: Calculation of Carr's index and Hausner ratio for set-3a

Starch: F3	Bulk	Avg Bulk	Tapped	Avg Tapped	Carr's's Index	Hausner Ratio
40:60	12 11.5 11	11.5	9 8.5 8	8.5	26.086	1.352
50:50	11.5 11 10.5	11	8.8 8.4 8	8.4	23.27	1.305
60:40	11.5 11 10.5	11	8.5 8 9	8.5	22.72	1.29
70:30	10.5 10 9.5	10	8.5 8 7.5	8	20	1.25

By plotting percentage ratio of starch 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'sindex of any set of excipients can be achieved.

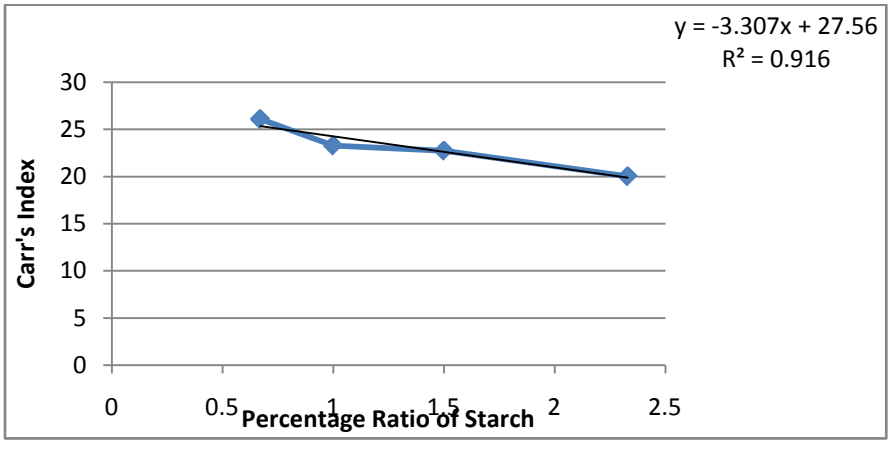

Figure 4.7: A percentage ratio of starch versus Carr's index graph

By plotting percentage ratio of starch 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 can be achieved.

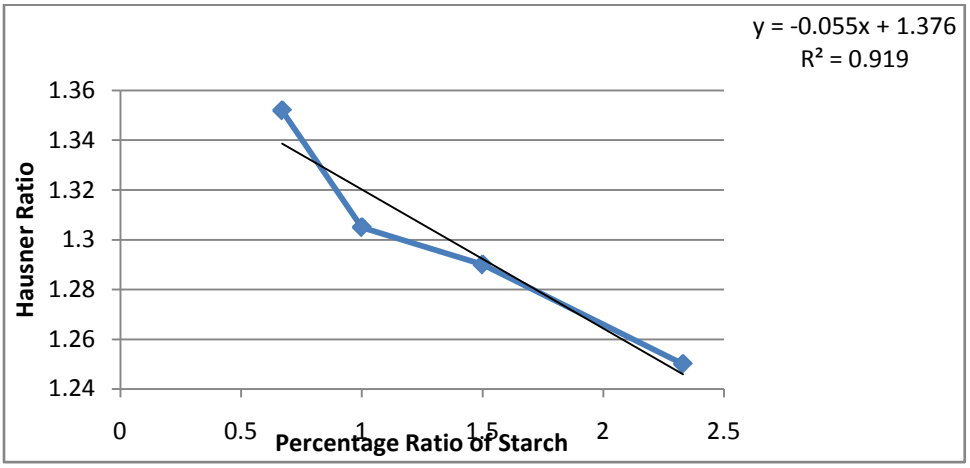

Figure 4.8: A percentage ratio of starch versus Hausner ratio graph

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

4.8 Table: Calculation of Angle of repose for set-3a

Starch: F3	Height (h)	AvgHeight (h)	Diameter (2r)	Avg Diameter (2r)	Radius (r)	Angle of Repose
40:60	2 1.7 1.4	1.7	5.2 4.8 4.4	4.8	2.4	35.311
50:50	2 1.85 1.70	1.85	5.5 5 4.5	5	2.5	36.53
60:40	2.5 1.9 1.3	1.9	5.5 5.1 4.7	5.1	2.55	36.785
70:30	2.5 2.1 1.7	2.1	5.5 5.2 4.9	5.2	2.6	38.927

By plotting percentage ratio of starch 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 can be achieved.

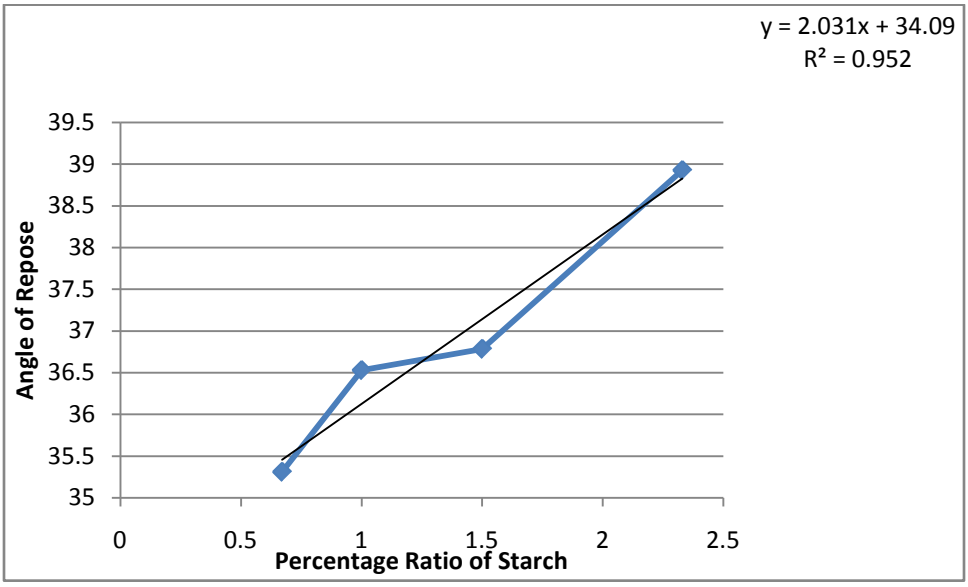

Figure 4.9: A percentage ratio of starch versus angle of repose graph

4.1.2.4 For set 3b:

The Carr's index and Hausner ratio of set-3b was calculated by their bulk volume and tapped volumes which were measured three times and the average value was taken. The observed value is given below:

4.9 Table: Calculation of Carr's index and Hausner ratio for set-3b

Lactose : F3	Bulk	Avg Bulk	Tapped	Avg Tapped	Carr's's Index	Hausner Ratio
45:55	11.5 11 10.5	11	8.5 8 7.5	8	27.27	1.375
55:45	11 10.5 10	10.5	8 7.5 7	7.5	28.57	1.4
65:35	10 9.5 9	9.5	7.5 7 6.5	7	26.315	1.357
75:25	9.5 9 8.5	9	7.5 7 6.5	7	22.22	1.285

By plotting percentage ratio of lactose 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 can be achieved.

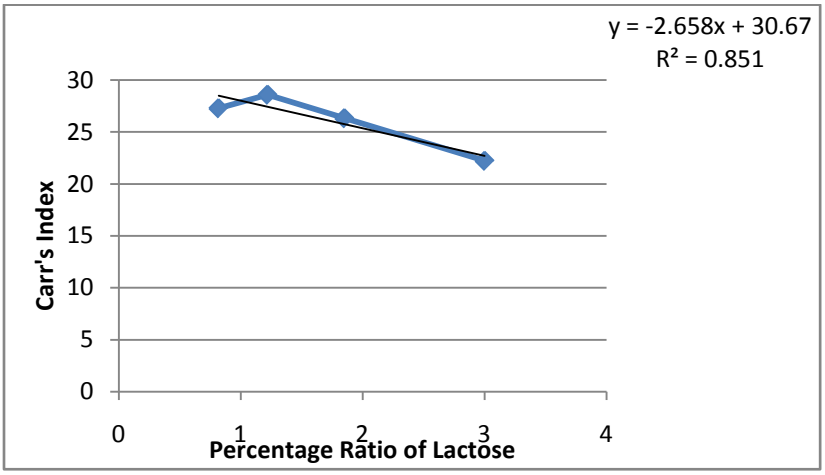

Figure 4.10: A percentage ratio of lactose versus Carr's index graph

By plotting percentage ratio of lactose 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 can be achieved.

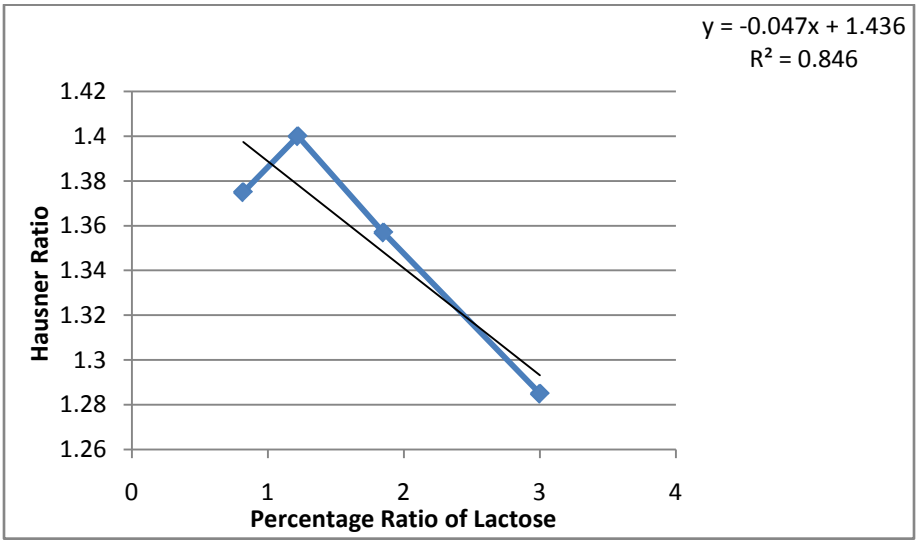

Figure 4.11: A percentage ratio of lactose versus Hausner ratio graph

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

4.10 Table: Calculation of Angle of repose for set-3b

Lactose : F3	**Height (h)**	**Avg Height (h)**	**Diameter (2r)**	**AvgDiameter (2r)**	**Radius (r)**	**Angle of Repose**
45:55	2 1.6 1.2	1.6	5.5 5 4.5	5	2.5	32.659
55:45	2 1.7 1.4	1.7	5.5 5.1 4.7	5.1	2.55	33.69
65:35	2 1.5 1	1.5	5 4.6 4.2	4.6	2.3	33.11
75:25	2.3 1.9 1.5	1.9	5 4.5 4	4.5	2.25	40.41

By plotting percentage ratio of lactose 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 can be achieved.

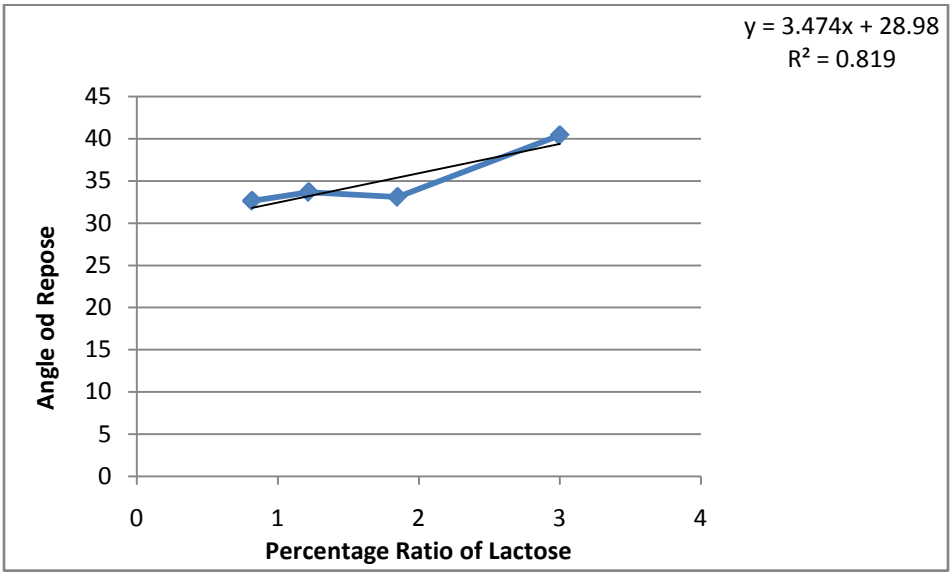

Figure 4.12: A percentage ratio of lactose versus angle of repose graph

4.1.2.5 For set 4a:

The Carr's index and Hausner ratio of set-4a was calculated by their bulk volume and tapped volumes which were measured three times and the average value was taken. The observed value is given below:

4.11 Table: Calculation of Carr's index and Hausner ratio for set-4a

Calcium phosphate : F4	Bulk	Avg Bulk	Tapped	Avg Tapped	Carr's's Index	Hausner Ratio
35:65	10 9.5 9	9.5	6 6.5 5.5	6	36.842	1.583
45:55	10 9.5 9	9.5	7 6.5 6	6.5	31.578	1.46
55:45	8.5 9.5 9	9	7 6.5 6	6.5	27.77	1.384
65:35	10 9.5 9	9.5	7 7 7	7	26.315	1.35

By plotting percentage ratio of calcium phosphate 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 can be achieved.

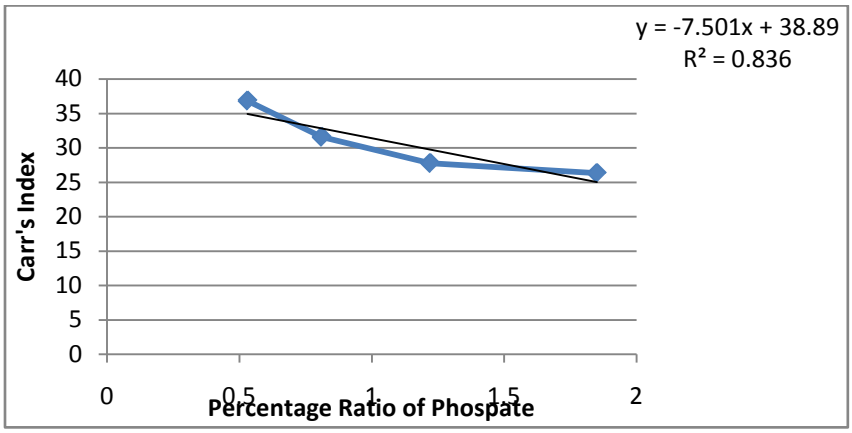

Figure 4.13: A percentage ratio of calcium phosphate versus Carr's index graph

By plotting percentage ratio of calcium phosphate 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 can be achieved.

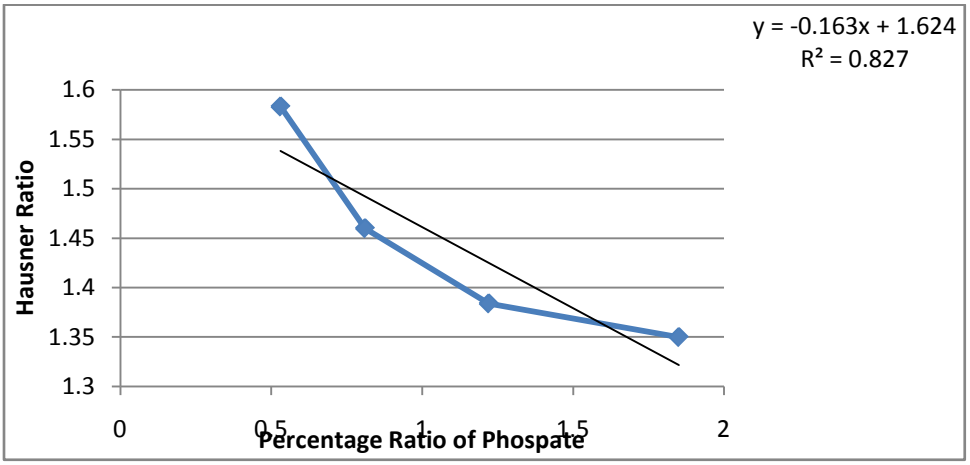

Figure 4.14: A percentage ratio of calcium phosphate versus Hausner ratio graph

The angle of repose of set-4a was calculated by their cone height and radius which were measured three times and the average value was taken. The observed value is given below:

4.12 Table: Calculation of Angle of repose for set-4a

Starch: F4	Height (h)	Avg Height (h)	Diameter (2r)	Avg Diameter (2r)	Radius (r)	Angle of Repose
35:65	2.2 1.8 1.4	1.8	5.4 4.9 4.5	4.9	2.45	36.304
45:55	2 1.5 1	1.5	6 5.5 5	5.5	2.75	33.50
55:45	2 1.7 1.4	1.7	5 4.7 4.4	4.7	2.35	35.882
65:35	2 1.6 1.2	1.6	5.5 5.2 4.9	5.2	2.6	25.8

By plotting percentage ratio of calcium phosphate 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 can be achieved.

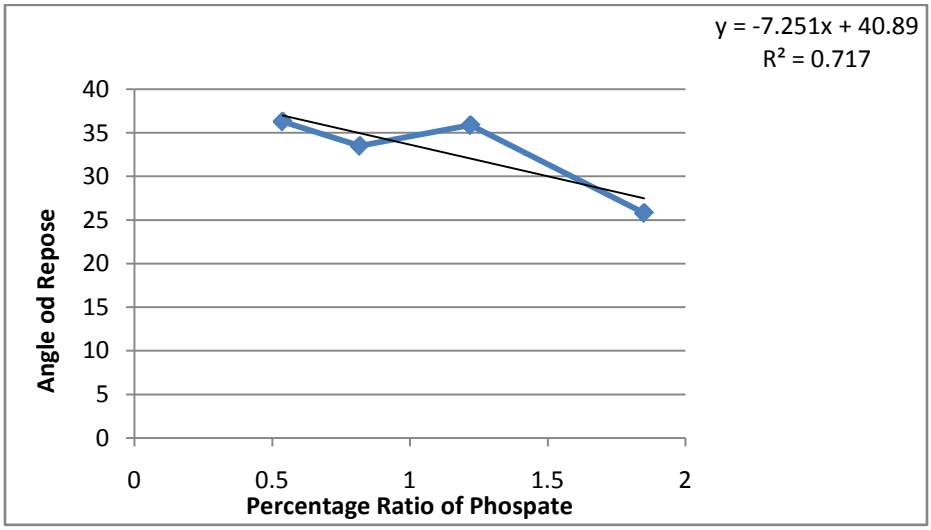

Figure 4.15: A percentage ratio of calcium phosphate versus angle of repose graph

4.1.2.6 For set 4b:

The Carr's index and Hausner ratio of set-4b was calculated by their bulk volume and tapped volumes which were measured three times and the average value was taken. The observed value is given below:

4.13 Table: Calculation of Carr's index and Hausner ratio for set-4b

Starch: F4	Bulk	Avg Bulk	Tapped	Avg Tapped	Carr's's Index	Hausner Ratio
30:70	10.5 10 9.5	10	7.5 7 6.5	7	30	1.428
40:60	9.5 9 8.5	9	6.7 6.3 6.5	6.3	29.8	1.426
50:50	10.5 10 9.5	10	7.5 7.2 6.9	7.2	27.8	1.388
60:40	11 10.5 10	10.5	8 7.6 7.2	7.6	27.3	1.381

By plotting percentage ratio of starch 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 can be achieved.

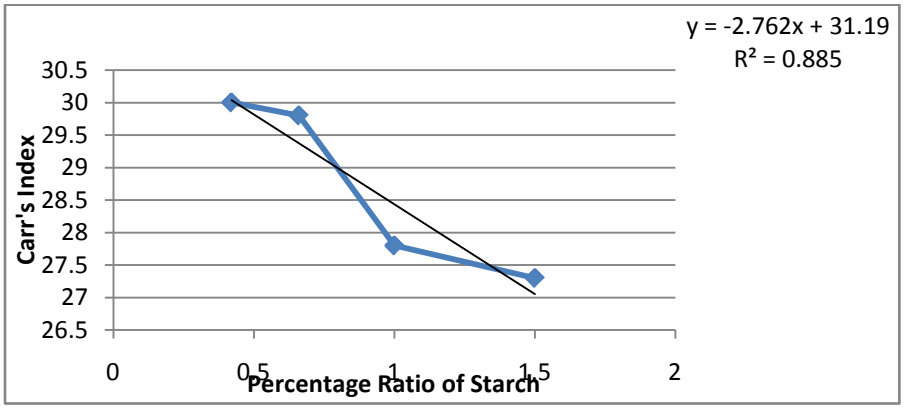

Figure 4.16: A percentage ratio of starch versus Carr's index graph

By plotting percentage ratio of starch 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 can be achieved.

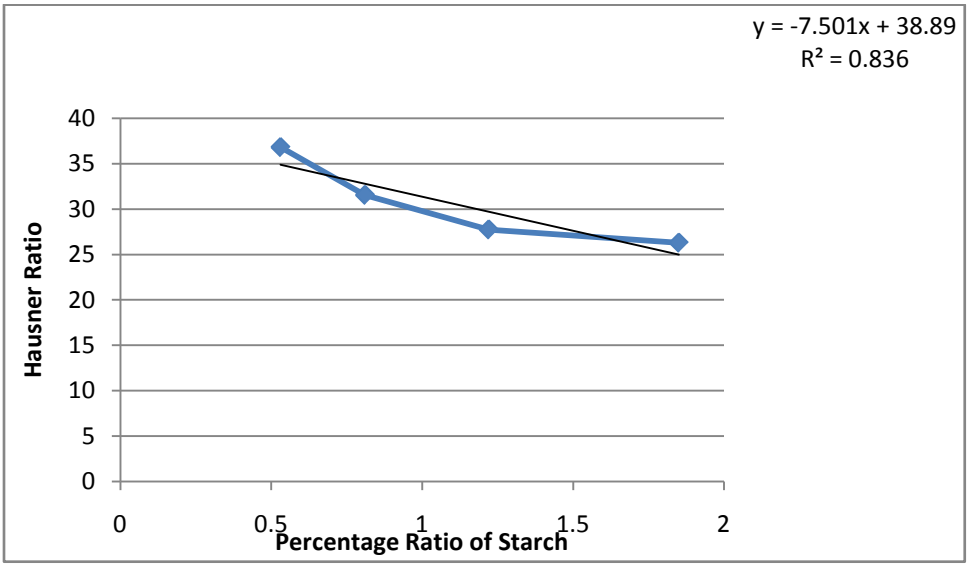

Figure 4.17: A percentage ratio of starch versus Hausner ratio graph

The angle of repose of set-4b was calculated by their cone height and radius which were measured three times and the average value was taken. The observed value is given below:

4.14 Table: Calculation of Angle of repose for set-4b

Starch: F4	Height (h)	AvgHeight (h)	Diameter (2r)	Avg Diameter (2r)	Radius (r)	Angle of Repose
30:70	1.5 1 0.5	1	5.4 4.9 4.4	4.9	2.45	22.203
40:60	1 0.9 0.9	1	5 5 5	5	2.5	21.8
50:50	2 1.5 1	1.5	4.5 5 5.5	5	2.5	30.96
60:40	2 1.8 1.6	1.8	5.2 4.8 4.4	4.8	2.4	36.869

By plotting percentage ratio of starch 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 can be achieved.

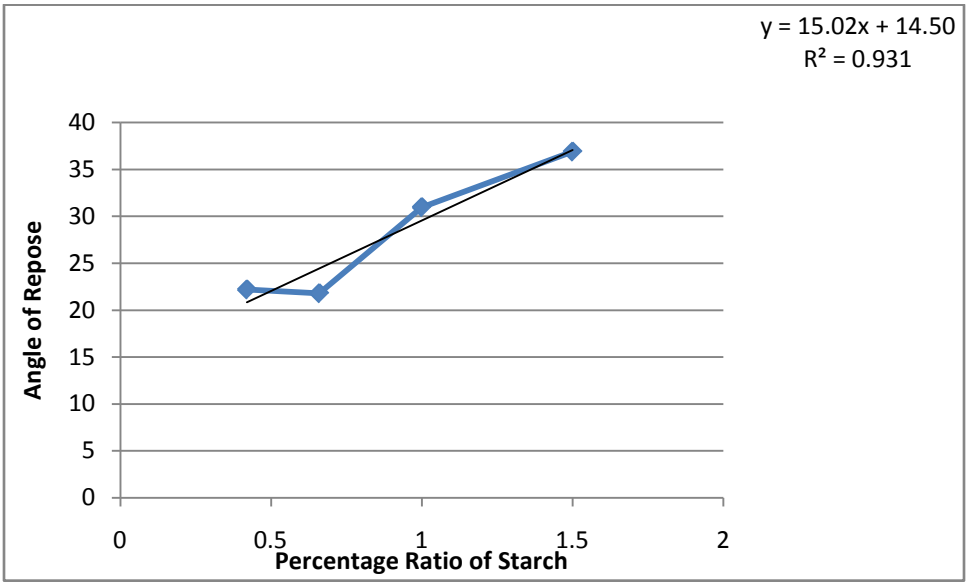

Figure 4.18: A percentage ratio of starch versus angle of repose graph

4.1.2.7 For set 5a:

The Carr's index and Hausner ratio of set-5a was calculated by their bulk volume and tapped volumes which were measured three times and the average value was taken. The observed value is given below:

4.15 Table: Calculation of Carr's index and Hausner ratio for set-5a

Lactose : F5	Bulk	Avg Bulk	Tapped	Avg Tapped	Carr's's Index	Hausner Ratio
50:50	11.5 11 10.5	11	8.5 8 7.5	8	24.7	1.375
60:40	10 9.5 9	9.5	7.4 7.2 7	7.2	24.052	1.319
70:30	10.5 10 9.5	10	7.35 7.15 6.95	7.15	28.5	1.398
80:20	11 10.5 10	10.5	7.5 7 6.5	7	33.33	1.55

By plotting percentage ratio of lactose 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 can be achieved.

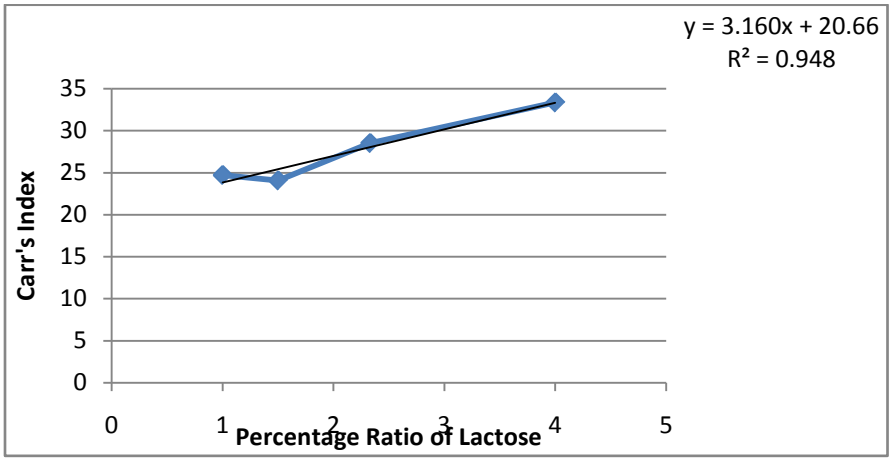

Figure 4.19: A percentage ratio of lactose versus Carr's index graph

By plotting percentage ratio of lactose 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 can be achieved.

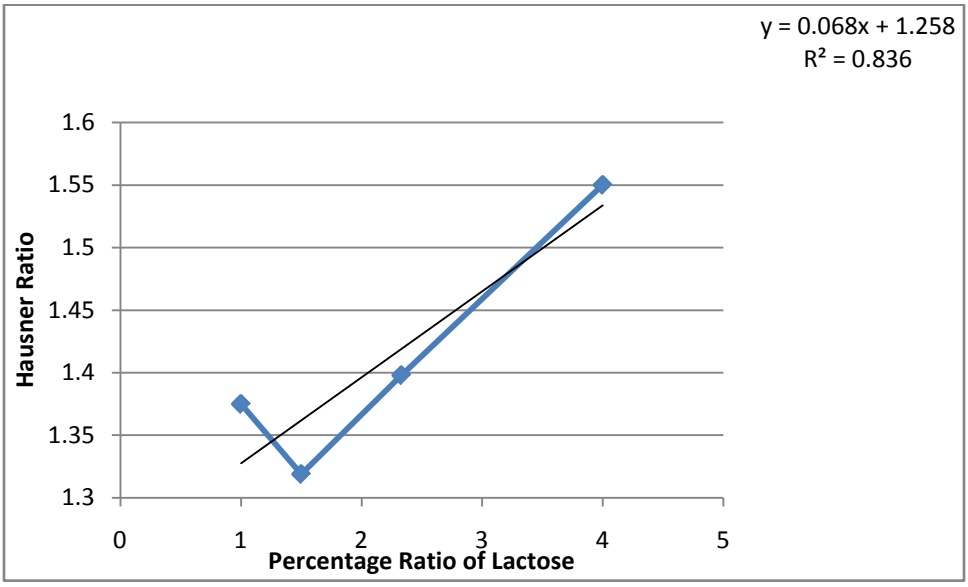

Figure 4.20: A percentage ratio of lactose versus Hausner ratio graph

The angle of repose of set-5a was calculated by their cone height and radius which were measured three times and the average value was taken. The observed value is given below:

4.16 Table: Calculation of Angle of repose for set-5a

Lactose : F5	Height (h)	Avg Height (h)	Diameter (2r)	Avg Diameter (2r)	Radius (r)	Angle of Repose
50:50	2 1.6 1.2	1.6	6 5.5 5	5.5	2.75	30.191
60:40	2 1.5 1	1.5	5.8 5.3 4.8	5.3	2.65	31.122
70:30	1.9 1.8 1.7	1.8	5.9 5.3 4.7	5.3	2.65	34.3
80:20	2 1.8 1.6	1.8	5.5 5 4.5	5	2.5	35.753

By plotting percentage ratio of lactose 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 can be achieved.

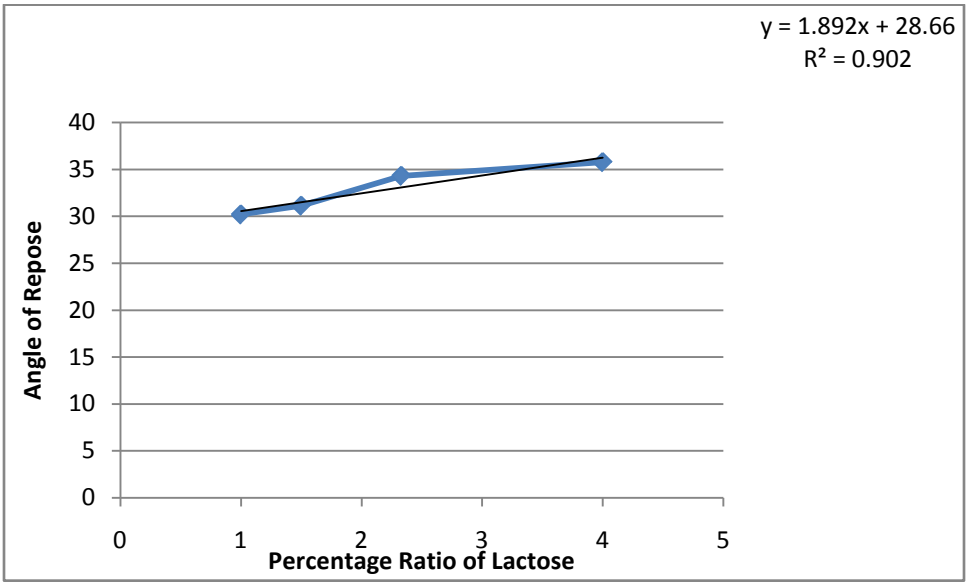

Figure 4.21: A percentage ratio of lactose versus angle of repose graph

4.1.2.8 For set 5b:

The Carr's index and Hausner ratio of set-5b was calculated by their bulk volume and tapped volumes which were measured three times and the average value was taken. The observed value is given below:

4.17 Table: Calculation of Carr's index and Hausner ratio for set-5b

Talc: F5	Bulk	Avg Bulk	Tapped	Avg Tapped	Carr's's Index	Hausner Ratio
25:75	13 12.5 12	12.5	8.8 8.6 8.7	8.6	30.8	1.315
35:65	11.5 11 10.5	11	8 7.55 7	7.6	31	1.46
45:55	11 10.5 10	10.5	7.4 7.3 7.2	7.3	30.5	1.438
55:45	10.5 10 9.5	10	7.5 7 6.5	7	30	1.428

By plotting percentage ratio of talc 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 can be achieved.

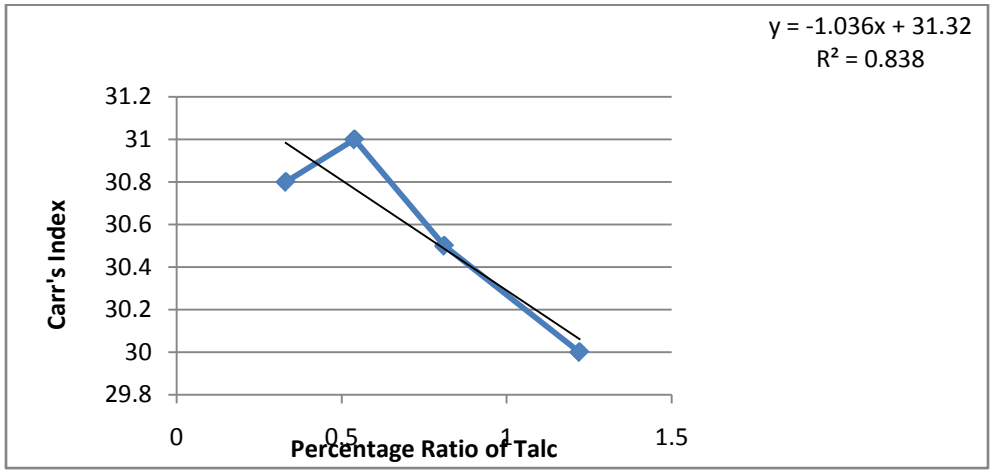

Figure 4.22: A percentage ratio of talc versus Carr's index graph

By plotting percentage ratio of talc 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 can be achieved

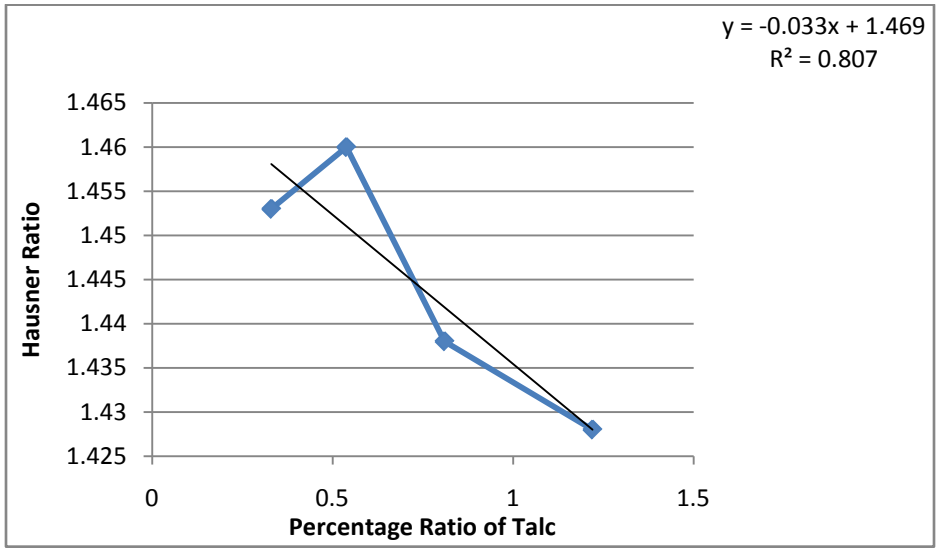

Figure 4.23: A percentage ratio of talc versus Hausner ratio graph

The angle of repose of set-5b was calculated by their cone height and radius which were measured three times and the average value was taken. The observed value is given below:

4.18 Table: Calculation of Angle of repose for set-5b

Talc: F5	Height (h)	Avg Height (h)	Diameter (2r)	Avg Diameter (2r)	Radius (r)	Angle of Repose
25:75	2.5 2 1.5	2	6 5.6 5.2	5.6	2.8	35.537
35:65	1.7 1.8 1.6	1.7	5.2 4.9 4.6	4.9	2.45	35.105
45:55	1.7 1.8 1.6	1.8	5.8 5.4 5	5.4	2.7	34.9
55:45	1.9 1.6 1.3	1.6	5 4.8 4.6	4.8	2.4	33.805

By plotting percentage ratio of talc 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 can be achieved.

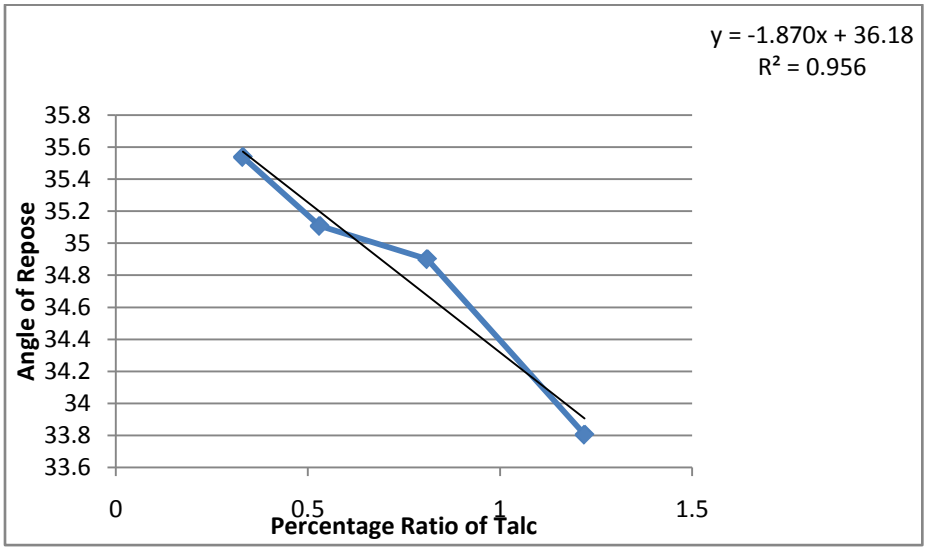

Figure 4.24: A percentage ratio of talc versus angle of repose graph

Chapter Five

DISCUSSION & CONCLUSION

5.1 DISCUSSION

This work was proposed to determine flow properties of different set of pharmaceutical excipients. 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. Diluents 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. 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 diluents. From these 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 ratio of diluents.

The research work has demonstrated that flow property of different ratio of diluents and formulas did not maintain the same rule. Sometimes the set of ratio having larger quantity of diluents showed better flow property, sometimes not. In fact the variation of results also 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 against variable ratio of different diluents was discussed below with some observed deviations. Moreover the most suitable ratio of diluents and a defined set of other excipients (formulas) are proposed that showed better flowability.

- In case of set-1, the calculated value (Table 4.3, 4.4) and graph (Figure 4.1, 4.2, 4.3) signified that, the mixture of ratio having high quantity of lactose showed better flow property than the other ratios as the values of the Carr's index, Hausner ratio and angle of repose gradually increased with the decreasing ratio of lactose in that mixture of formula. It was stated above that the lower the value of Carr's index, Hausner ratio and angle of repose, the better the flow property. So for this set, the most desirable flow was obtained when the ratio of lactose and formula-1 is 75%:25%. From table 4.3, it can also be said that the values of Carr's index and Hausner ratio lied in between the fair range (Table 1.2). The measured value of angle of repose (Table 4.4) for 75%:25% (lactose: F1) also lied in between the fair range according to Table 1.1.

- In case of set-2, the relation between the diluents (calcium phosphate) and formula (F2) did not follow any sequential relationship. The calculated value (Table 4.5) and graph (Figure 4.4, 4.5) signified that, the most desirable flow property was observed in the ratio of 65%:35% (calcium phosphate: F2) when Carr's index and Hausner ratio were calculated. But the measured value for angle of repose was different. From Table 4.6, the flowability decreases with the increasing quantity of diluents (calcium phosphate) added. So in these case, 55%:45% (calcium phosphate: F2) ratio showed better flow property (Figure 4.6) than the other one. From table 4.4, it can also be said that for the ratio of 65%:35%, the value of Carr's index lied in between the poor range and the value of Hausner ratio lied in between the fair range (Table 1.2). The measured value of angle of repose (Table 4.6) for 55%:45% (calcium phosphate: F1) lied in between the fair range according to Table 1.1.

- In case of set-3a, the calculated value (Table 4.7) and graph (Figure 4.7, 4.8) signified that, the mixture of ratio having high quantity of starch showed better flow property than the other ratios as the values of the Carr's index and Hausner ratio gradually increased with the decreasing ratio of starch in that mixture of

formula. In these case, 70%:30% ratio (starch: F3) showed better flowability and the values lied in between the fair range according to Table 1.2. When the measurement of angle of repose is concerned (Table 4.8, Figure 4.9), any relationship could not be stated as the values were not regulated sequentially. 50%:50% (starch: F3) ratio was proposed most suitable in these case and the value lied in between the good range (Table 1.1).

- In case of set-3b, the calculated value (Table 4.9) and graph (Figure 4.10, 4.11) signified that, the mixture of ratio having high quantity of lactose showed better flow property than the other ratios as the values of the Carr's index and Hausner ratio gradually increased with the decreasing ratio of lactose in that mixture of formula. In these case, 75%:25% ratio (lactose: F3) showed better flowability and the values lied in between the passable range according to Table 1.2. When the measurement of angle of repose is concerned, the value (Table 4.10, Figure 4.12) indicated that the flow property decreases with the increasing amount of diluents (lactose) added and the most suitable ratio is 45%:55% (lactose: F3). The observed value lied in between the good range according to Table 1.1.

- In case of set-4a, the calculated value (Table 4.11) and graph (Figure 4.13, 4.14) signified that, the mixture of ratio having high quantity of calcium phosphate showed better flow property than the other ratios as the values of the Carr's index and Hausner ratio gradually increased with the decreasing ratio of calcium phosphate in that mixture of formula. In these case, 65%:35% ratio (calcium phosphate: F4) showed better flowability and the values lied in between the poor range according to Table 1.2. When the measurement of angle of repose is concerned (Table 4.12, Figure 4.15), any relationship could not be stated as the values were not regulated sequentially. 55%:45% (calcium phosphate: F4) ratio was proposed most suitable in these case and the value lied in between the excellent range (Table 1.1). In this case, the result fluctuated between Carr's index, Hausner ratio and angle of repose.

- In case of set-4b, the calculated value (Table 4.13) and graph (Figure 4.16, 4.17) signified that, the mixture of ratio having high quantity of starch showed better flow property than the other ratios as the values of the Carr's index and Hausner ratio gradually decreased with the increasing ratio of starch in that mixture of formula. 60%:40% (starch: F4) was considered the most suitable ratio in case of measuring Carr's index and Hausner ratio and the value lied in the poor range (Table 1.2). According to angle of repose measurement (Table 4.14, Figure 4.18), 40%:60% ratio (starch: F4) was considered most suitable among others and the value lied in excellent range (Table 1.1).

- In case of set-5a, the values of Carr's index and Hausner ratio varied for different ratios. 60%:40% (lactose: F5) was considered most suitable that showed better flowability according to the calculated value of Carr's index and Hausner ratio (Table 4.15, Figure 4.19, 4.20). The values of the Carr's index and Hausner ratio for 60%:40% (lactose: F5) lied in between the passable range (Table 1.2). But when angle of repose is concerned (Table 4.16, Figure 4.21), the flowability decreases with the increasing ratio of lactose and the value of proposed ratio 50%:50% (lactose: F5) lied in between good range according to Table 1.1.

- In case of set-5b, the values of Carr's index and Hausner ratio varied for different ratios. According to the calculated value of Carr's index (Table 4.17, Figure 4.22) 55%:45% (talc: F5) was considered most suitable ratios among others that showed better flowability and the value lied in poor range (Table 1.2). In case of Hausner ratio (Table 4.17, Figure 4.23), 25%:75% (talc: F5) was considered most favorable and the value lied in passable range (Table 1.2). When the measurement of angle of repose is concerned, the value (Table 4.18, Figure 4.24) indicated that the flow property increases with the increasing amount of diluents (talc) added and the most suitable ratio is 55%:45% (talc: F5). The observed value lied in between the good range according to Table 1.1.

5.2 CONCLUSION

Pharmaceutical excipients are considered as a vital part of any dosage form formulation. Without these ingredient 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. The study was conducted to observe the flow characteristics of different combination of excipients in different ratios. Variation of flow property of different set of formulas of excipients against variable ratio of different diluents was observed and the most suitable ratio of diluents and a defined set of other excipients (formulas) were proposed that showed better flowability. Moreover, the plotted graphs and the equations for each set of formula were obtained which can be used to predict the flow property of these formulas with different ratio of diluents. This would help any future query about the flow property of any set of excipients in different ratios.

Chapter Six

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