DETERMINATION OF VARIATION IN FLOW PROPERTY OF DIFFERENT FORMULAS OF MAGNESIUM STEARATE ALONG WITH PROPRANOLOL AND AMLODIPINE

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

Submitted By

Tasmia Hoque

ID: 2012-1-70-051

Supervisor

Mr. Md. Anisur Rahman

Senior lecturer, Department of Pharmacy

East West University

Department of Pharmacy,

East West University

DEDICATION

This Research Paper Is Dedicated To My Beloved Mother, Who Is My Biggest Inspirations….

DECLARATION BY THE CANDIDATE

I, Tasmia Hoque, hereby declare that this dissertation, entitled **"DETERMINATION OF VARIATION IN FLOW PROPERTY OF DIFFERENT FORMULAS OF MAGNESIUM STEARATE ALONG WITH PROPRANOLOL AND AMLODIPINE"** submitted to the Department of Pharmacy, East West University, in the partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Honors) is a genuine & authentic research work carried out by me. The contents of this dissertation, in full or in parts, have not been submitted to any other institute or University for the award of any degree or Diploma of Fellowship.

_____

Tasmia Hoque

ID: 2012-1-70-051

Department of Pharmacy

East West University

Aftabnagar, Dhaka.

CERTIFICATION BY THE SUPERVISOR

This is to certify that the dissertation, entitled **"DETERMINATION OF VARIATION IN FLOW PROPERTY OF DIFFERENT FORMULAS OF MAGNESIUM STEARATE ALONG WITH PROPRANOLOL AND AMLODIPINE"** is a bona fide research work done by Tasmia Hoque (ID: 2012-1-70-051), in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

Mr. Md. Anisur Rahman (Supervisor)
Senior Lecturer
Department of Pharmacy
East West University
Aftabnagar, Dhaka.

Mohammed Faisal Bin Karim
(Co-Supervisor)
Senior Lecturer
Department of Pharmacy
East West University
Aftabnagar, Dhaka

ENDORSEMENT BY THE CHAIRPERSON

This is to certify that the dissertation, entitled **"DETERMINATION OF VARIATION IN FLOW PROPERTY OF DIFFERENT FORMULAS OF MAGNESIUM STEARATE ALONG WITH PROPRANOLOL AND AMLODIPINE"** is a bona fide research work done by Tasmia Hoque (ID: 2012-1-70-051), under the guidance of Mr. Md. Anisur Rahman, in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

_____

Dr. Shamsun Nahar Khan

Associate Professor & Chairperson

Department of Pharmacy

East West University

Aftabnagar, Dhaka.

ACKNOWLEDGEMENTS

Above all, I express my gratitude to Almighty Allah for all the bounties granted to me and only with his guidance and help this achievement has become possible.

It is my pleasure and proud privilege to express my heartiest regards and gratitude to my respected teacher and supervisor **Mr. Md. Anisur Rahman**, Senior Lecturer, Department of Pharmacy, East West University, for his expert supervision, constructive criticism, valuable advice, optimistic counseling, constant support & continuous backup and encouragement throughout every phase of the project as well as to prepare this dissertation.

I would like to extend my cordial gratitude to my co-supervisor **Mr. Mohammed Faisal Bin Karim**, Senior Lecturer, Department of Pharmacy, East West University for his constant inspiration and whole hearted cooperation.

I would also like to put forward my most sincere regards and profound gratitude to **Dr. Shamsun Nahar Khan**, Associate Professor & Chairperson, Department of Pharmacy, East West University, for giving me the opportunity to conduct such an interesting project and for facilitating a smooth conduction of my study.

I owe special thanks to my fellow research group members Jarrin Rashid, Tasnim Iffat and Umme Habiba, near and dear ones who offered encouragement, information, inspiration and assistance during the period of constructing the research report.

Last but not the least, I would like to thanks my family and friends for their care and encouragement during my research work.

ABSTRACT

This work was performed to determine flow properties of different set of some important pharmaceutical excipients that are most commonly used for the directly compressible tablets, dry powders, powder for suspensions etc. This study was also done to search for some equations which can predict the flow property of any set of excipients with different ratio of anti adherent (Mg stearate) along with propranolol and amlodipine. Different parameters to determine flow property such as Compressibility index, Hausner ratio, and angle of repose were observed for them. Anti adherent was mixed with these prepared formulas in different specific and justified ratio. The values of Carr's index, Hausner ratio and angle of repose were plotted against the percentage ratios of anti adherent. The study showed a linear relationship with different ratios of mixture and flow property measuring parameters. From these graphs the straight-line equation for each set of formula were obtained. Moreover the most suitable ratio of anti adherent and a specific set of other excipients were proposed that showed better flow property.

Key words: Flow property, angle of repose, hausner ratio, carr's index, propranolol, amlodipine.

List of Content

List of Tables

List of Figures

CHAPTER 1

INTRODUCTION

1.1 Introduction:

The purpose of the research was to determine the flow characteristics of different active pharmaceutical ingredient (API) with different formulations of excipients. In this research two classes of API was used. One was amlodipine which is a calcium channel blocker and another one was propranolol which is a beta-adrenergic antagonist. At first different ration of excipients were made and then the flow property of those excipients were measured. After that different API were mixed to see whether there was any change in the flow properties. Then individual flow characteristics were measured using different parameters, for example, angle of repose, Carr's index or compressibility index and Hausner's ratio.

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 different formulatios of excipients from plotting a standard curve. For accurate result, the experiments were done five times and all the guidelines were followed.

1.2 Powder flow property: (Freemantech, 2013)

Powder flow ability 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, flow ability is not an inherent material property at all. Flow ability 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.

1.2.1 Importance of Flow property:

- 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.
- Different stages of manufacturing procedure such as blending, transfer, storage, compaction all depend on good powder flowability.
- Designing and troubleshooting mass flow hoppers requires the measurement of powder flow.

- ❖ Tableting operations require excipients with the desired flow, physical and mechanical properties.
- ❖ Measurement of flow property is important phenomena as uniform flow of solid mixtures is one of the most important considerations in solid dosage formulation.
- ❖ 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.
- ❖ 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: (Freemantech, 2013).

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

- ✓ Particle size & Size distribution:

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

- ✓ Particle shape:

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

- ✓ Moisture:

The effect of moisture on flowability of particles varies from powder to powder. The particles become cohesive due to moisture absorption. In presence of excessive moisture, the

powder shows poor flowability. In this experiment, I have used desiccant in different powder bulk to remove the moisture content from the powder and maximize the flow characteristic of the powders used.

✓ Electrostatic effects:

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

✓ Powder cohesion and storage compaction:

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

✓ Effect of temperature:

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

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 (US 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).

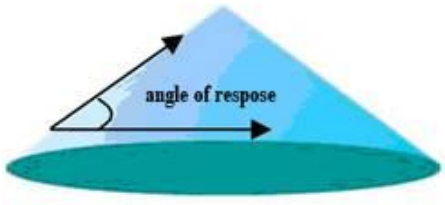

*Figure 1.1: Angle of repose (*Merriam, 2013)

When bulk granular materials are poured onto a horizontal surface, a conical pile will form. The internal angle between the surface of the pile and the horizontal surface is known as the angle of repose and is related to the density, surface area and shapes of the particles, and the coefficient of friction of the material. It also depends on gravity. Material with a low angle of repose forms flatter piles than material with a high angle of repose.

The angle of repose has been used to characterize the flow properties of powders. It is related to interparticulate friction or movement between particles. Results were only considered valid when a symmetrical cone of powder was formed (Copleyscientific, 2012).

1.1 Table: Relation between flow properties and angle of repose

Flow property	Angle of repose (degrees)
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Very, very poor	>66

Factors that influence the angle of repose:

- Decrease the particle size, higher angle of repose
- Fine particles (up to 15%), increase angle of repose
- Lubricants at low concentration, lower the angle of repose
- Rough and irregular surface, higher angle of repose (Authorstream, 2013).

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

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

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

1.2.3.2 Compressibility index and Hausner ratio (Vinensia, 2013).

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 = $$\frac{100(V_o - V_f)}{V_o}.$$

Where,

Vo = Bulk volume

Vf = 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.

Hausner ratio can be calculated by following formula:

$$\text{Hausner ratio} = \frac{V_0}{V_f}$$

Where,

Vo = Bulk volume and Vf = Tapped volume

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

Compressibility index (percent)	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 (Vinensia, 2013)

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).

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:

- ✓ Antiadherents
- ✓ Binders
- ✓ Coatings
- ✓ Disintegrants
- ✓ Lubricants
- ✓ Glidants
- ✓ Sorbents
- ✓ Preservatives

- ✓ Fillers
- ✓ Sweeteners
- ✓ Flavours

1.3.1.1.1 Diluents: (Pformulate, 2000)

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.

Influence of diluents on bioavailability:

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

Influence of diluents on incompatibility:

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

Tablet diluents or fillers can be divided into three categories:

- ➢ 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

- Inorganic materials: Calcium phosphates, Anhydrous Dibasic Calcium Phosphate, Dibasic Calcium Phosphate, Tribasic Calcium Phosphate.

- 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: (Pformulate, 2000).

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
- ✓ 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
- ✓ polyvinylpyrrolidone (PVP)

1.3.1.1.5 Antiadherent: (Drugtopics, 2008).

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.

1.3.1.1.6 Miscellaneous:

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

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

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

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

- Flavorants: These are incorporated into the formulation to improve the flavor or give a pleasant taste to the formulation. Flavoring agents are mostly restricted to the formulations in which are intended to be released in the mouth or chewable tablets. They are usually added in along with the granules.

1.4 Excipients used in the experiment: (Drugtopics, 2008)

1.4.1 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.

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

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

- Molecular weight: 50000–160000

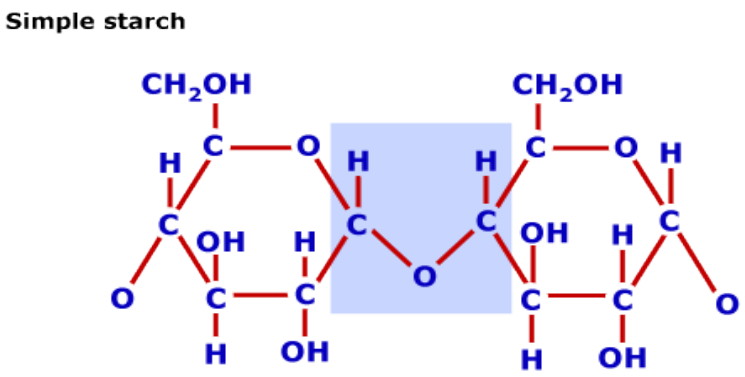

Fig 1.2: Starch (Drugtopics, 2008).

1.4.1.1 Functional Category:

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

1.4.1.2 Applications in Pharmaceutical Formulation or Technology:

Starch is used as an excipient primarily in oral solid-dosage formulations where it is utilized as a binder, diluent, and disintegrant.

As a diluent, starch is used for the preparation of standardized triturates of colorants or potent drugs to facilitate subsequent mixing or blending processes in manufacturing operations. Starch is also used in dry-filled capsule formulations for volume adjustment of the fill matrix.

In tablet formulations, freshly prepared starch paste is used at a concentration of 5–25% w/w in tablet granulations as a binder. Selection of the quantity required in a given system is determined by optimization studies, using parameters such as granule friability, tablet friability, hardness, disintegration rate, and drug dissolution rate.

Starch is one of the most commonly used tablet disintegrants at concentrations of 3–15% w/w. However, unmodified starch does not compress well and tends to increase tablet friability and capping if used in high concentrations. In granulated formulations, about half the total starch content is included in the granulation mixture and the balance as part of the final blend with the dried granulation.

Starch is also used in topical preparations; for example, it is widely used in dusting powders for its absorbency, and is used as a protective covering in ointment formulations applied to the skin. Starch mucilage has also been applied to the skin as an emollient, has formed the base of some enemas, and has been used in the treatment of iodine poisoning. (Rowe, Sheskey, Owen, 2005)

1.4.2 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.

- Empirical Formula: C36H70MgO4
- Molecular Weight: 591.34

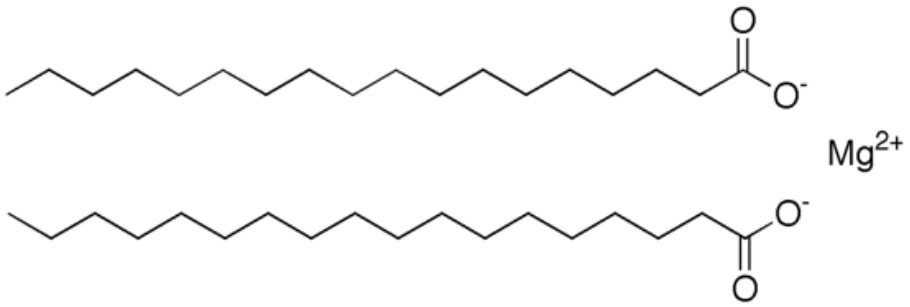

Fig 1.3: Mg Stearate (Rowe, Sheskey, Owen, 2005)

1.4.2.1 Functional Category:

- ✓ Tablet and capsule lubricant.

1.4.2.2 Applications in Pharmaceutical Formulation or Technology:

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams. (Rowe, Sheskey, Owen, 2005)

1.4.3 Carboxy methyl cellulose (CMC):

Carboxymethylcellulose appears as white, fibrous, free-flowing powder, and is used commonly as an FDA-approved disintegrant in pharmaceutical manufacturing. Disintegrants facilitate the breakup of a tablet in the intestinal tract after oral administration. Without a disintegrant, tablets may not dissolve appropriately and may effect the amount of active ingredient absorbed, thereby decreasing effectiveness. Carboxymethylcellulose is available in different salt forms, such as sodium or calcium. (Drugs.com, 2011)

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

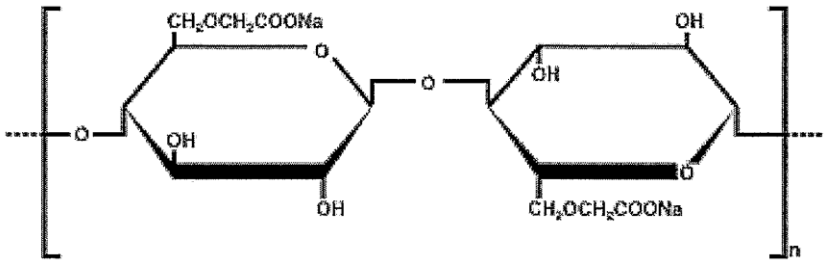

Fig 1.4: Carboxymethylcellulose (Rowe, Sheskey, Owen, 2005)

1.4.3.1 Functional Category:

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

1.4.3.2 Applications in Pharmaceutical Formulation or Technology:

The main use of carboxymethylcellulose calcium is in tablet formulations, where it is used as a binder, diluent, and disintegrant. Although carboxymethylcellulose calcium is insoluble in water, it is an effective tablet disintegrant as it swells to several times its original bulk on contact with water. Concentrations up to 15% w/w may be used in tablet formulations; above this concentration, tablet hardness is reduced.

Carboxymethyl cellulose calcium is also used in other applications similarly to Carboxymethyl cellulose sodium; for example, as a suspending or viscosity increasing agent in oral and topical pharmaceutical formulations. Carboxymethyl cellulose calcium is also used in modern wound dressings for its water absorption, retention and hemostatic properties. (Rowe, Sheskey, Owen, 2005)

1.4.4 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. 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).

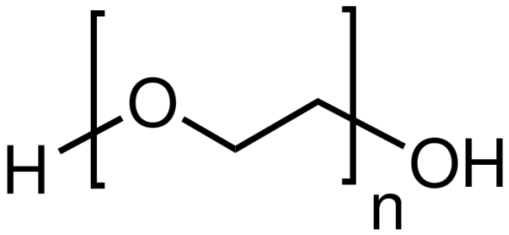

Fig 1.5: Polyethylene glycol (Dow, 2011)

1.4.5 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.

1.5 Active Pharmaceutical Ingredient:

1.5.1 Amlodipine: (Drugbank, 2005)

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

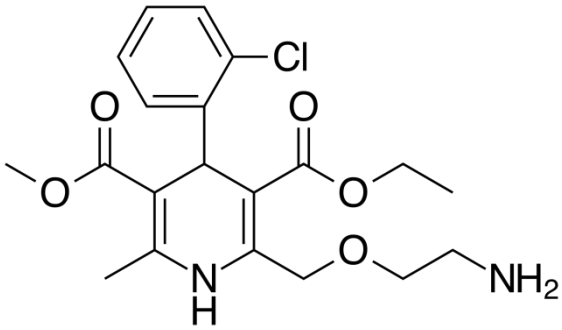

Fig 1.6: Amlodipine (Dow, 2011)

1.5.1.1 Indication:

- ✓ For the treatment of hypertension and chronic stable angina.

1.5.1.2 Pharmacodynamics: (Drugbank, 2005)

Amlodipine belongs to the dihydropyridine (DHP) class of calcium channel blockers (CCBs), the most widely used class of CCBs. There are at least five different types of calcium channels in Homo sapiens: L-, N-, P/Q-, R- and T-type. It was widely accepted that DHP CCBs target L-type calcium channels, the major channel in muscle cells that mediate contraction; however, some studies have indicated that amlodipine also binds to and inhibits N-type calcium channels. Similar to other DHP CCBs, amlodipine binds directly to inactive L-type calcium channels stabilizing their inactive conformation. Since arterial smooth muscle depolarizations are longer in duration than cardiac muscle depolarizations, inactive channels are more prevalent in smooth muscle cells. Alternative splicing of the alpha-1 subunit of the channel gives amlodipine additional arterial selectivity. At therapeutic sub-toxic concentrations, amlodipine has little effect on cardiac myocytes and conduction cells.

1.5.1.3 Mechanism of action:

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

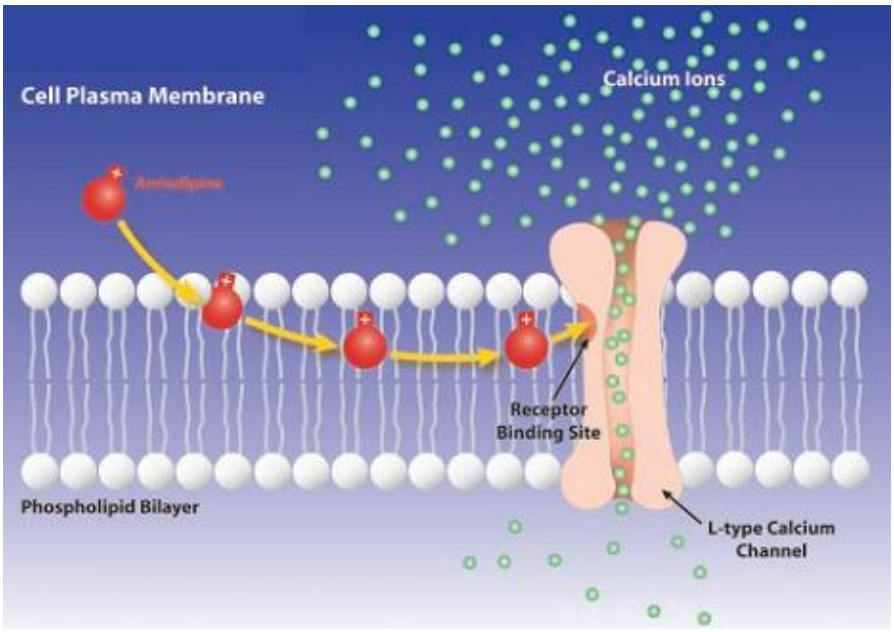

Fig 1.7: Mechanism of action of Amlodipine (Drugbank, 2005)

1.5.1.4 Adverse effects:

Adverse side effects of the use of amlodipine may include:

- Common and dose-related: peripheral edema (5.1%), dizziness (2.6%), palpitations (2.1%), flushing (1.5%)
- Common, not dose-related: fatigue (4.5%), nausea (2.9%), abdominal pain (1.6%), somnolence (1.4%)
- Rare (less than 1% incidence): blood disorders, impotence, depression, insomnia, tachycardia, or gingival enlargement, hepatitis, jaundice.

1.5.2 Propranolol: (drugbank, 2005)

1.5.2.1 Description:

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

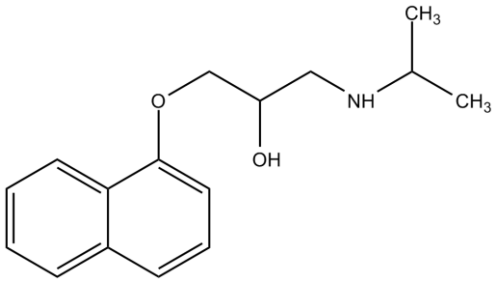

Fig 1.8: Propanolol (drugbank, 2005)

1.5.2.2 Mechanism of action:

Propranolol is a nonselective beta blocker; that is, it blocks the action of epinephrine and norepinephrine on both β_1- and β_2-adrenergic receptors. It has little intrinsic sympathomimetic activity, but has strong membrane stabilizing activity (only at high blood concentrations, e.g.

overdosage). Propranolol has inhibitory effects on the norepinephrine transporter and/or stimulates norepinephrine release. Since propranolol blocks β-adrenoceptors, the increase in synaptic norepinephrine only results in α-adrenergic activation, with the α1-adrenoceptor being particularly important for effects observed in animal models. Therefore, it can be looked upon as an indirect α1 agonist, as well as a β antagonist.

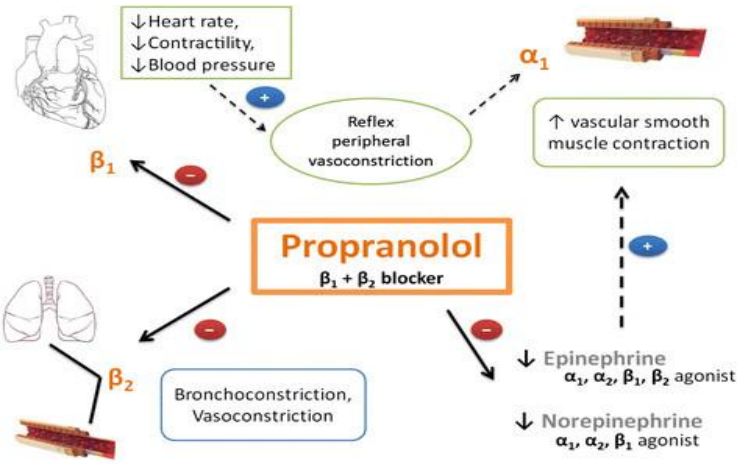

Fig 1.9: Mechanism of action of propanolol (drugbank, 2005)

1.5.2.3 Pharmacokinetics:

Propranolol is rapidly and completely absorbed, with peak plasma levels achieved about 1–3 hours after ingestion. Coadministration with food appears to enhance bioavailability. Despite complete absorption, propranolol has a variable bioavailability due to extensive first-pass metabolism. Hepatic impairment therefore increases its bioavailability. The main metabolite 4-hydroxypropranolol, with a longer half-life (5.2–7.5 hours) than the parent compound (3–4 hours), is also pharmacologically active.

Propranolol is a highly lipophilic drug achieving high concentrations in the brain. The duration of action of a single oral dose is longer than the half-life and may be up to 12 hours, if the single dose is high enough (e.g., 80 mg). Effective plasma concentrations are between 10 and 100 mg/l. Toxic levels are associated with plasma concentrations above 2000 mg/l.

1.5.2.4 Adverse effects:

Due to the high penetration across the blood-brain barrier, lipophilic beta blockers such as propranolol and metoprolol are more likely than other less lipophilic beta blockers to cause sleep disturbances such as insomnia and vivid dreams and nightmares.

Adverse drug reactions (ADRs) associated with propranolol therapy are similar to other lipophilic beta blockers. (drugbank, 2005)

CHAPTER 2

LITERATURE REVIEW

2.1 LITERATURE REVIEW:

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

In the year 1965, at firth Gold and Palermo took took an initiative to study the antistatic properties of tablet lubricants such as magnesium stearate, polyethylene glycol 4000, sodium lauryl sulfate and talc. From the data they found that these lubricants have the ability to lower the accumulation of static charges which results the flow of material through a tablet hopper. Their study showed that different highly static materials influence the antistatic properties of these lubricants. The antistatic effectiveness is decreased, if the concentration of lubricant gets lower. (Gold and Palermo, 1965)

Just in the next year, Gold with other three researchers (Gold et al., 1966) they used glidants and compared the results obtained by the measurement of angle of repose. 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 20oC

and 50% or 85% relative humidity of 500 mg acetylsalicylic acid. Their result showed that knowledge of the properties and interactions of drug, directly compressible excipients and other tablet vehicles makes possible the formulation and compression of different particle size acetylsalicylic acid powders into good quality tablets.

After three years, in another experiment in 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. At last they have come to a decision that the angle of repose and Hausner ratio measurements indicated a connection between the internal forces of friction and cohesion of the different sized powders and the tensile strength of compacts formed from them.

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

Then subsequent to seven year later, Tan and Newton (1990) worked on five pharmaceutical excipients in the middle of 1990 and found that the flowability of size fractions of five pharmaceutical excipients was related to their capsule filling performance. They used angular, packing and shear tests, the samples were ranked in different relative orders of flowability. They saw that there was a major correlation between the values of coefficient of variation and the flow parameters of Carr’s compressibility, Hausner’s's ratio, angle of repose, Kawakita's equation

constant and Jenike's flow factor. They also saw that coefficient of variation was also related to the variation in the compression stress and the coefficient of variation of the powder bed bulk density.

Then after four years Kamath, Puri and Manbeck (Kamath et al., 1994) using the Jenike shear testing, measured the flow properties such as cohesion and slope of the yield of wheat flour at various moisture contents 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.

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

The next year, in middle of 1995, Amidon and Houghton (1995) worked on the effects of moisture on the mechanical and powder flow properties of microcrystalline cellulose and finally they found powder flow was shown to decrease with increasing moisture content.

In the same year the effect of eleven pharmaceutical excipients with Avicel PHI02 SCG was investigated by two scientists, Flemming and Mielck (Flemming and Mielck, 1995). 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.

In the next year, 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. They found that 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 afterward 2000, Podczeck and Newton (2000) in their research paper studied Granulated powdered cellulose in terms of powder bulk properties and capsule filling performance on a tamp-filling machine with and without the addition of a range of concentrations of magnesium stearate. They found that Carr's compressibility reached its minimum value at 0.4% magnesium stearate signifying an improvement of powder flow compared to the unlubricated material. They also found that shear cell measurements and the use of a powder rheometer specified that the addition of 0.2% magnesium stearate and more impairs powder flow.

In the same year, Taylor his research fellows (Taylor et al. 2000) worked on the flow properties of typical tablet and capsule formulation excipients, active compounds as well as representative formulation blends were tested with current and novel flow measurement techniques to identify a reliable bench test to measure powder flow as a screening method in early tablet and capsule formulation development. Test methods used by them were vibrating spatula, critical orifice, and angle of repose, compressibility index, and avalanching analysis. They established empirical composite index and ranked powder flow in accordance with formulator experience. The data that they found were not reproducible from vibrating spatula and avalanching methods.

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 the subsequently year 2001, Hancock and his team determined the powder flow and compact mechanical properties of two recently developed matrix-forming polymers. The polymers were cross-linked high-amylose starch and poly acrylic acid. They compared the properties of polymers with those of two established matrix-forming polymers, hydroxypropyl methylcellulose and hydroxypropyl cellulose. They found that the particle morphology, size distribution and true density of the four materials were quite different as well as they exhibited quantifiable performance differences with respect to powder flow, compact ductility, compact elasticity and compact tensile strength. (Hancock et al., 2001)

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.

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

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

In the same year, Nagel and Peck (Nagel and Peck, 2003) evaluated the effect of pharmaceutical excipients on properties affecting tablet production. 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.

In the same year 2004, Bhattachar and his research fellows (Bhattachar et al., 2004) studied on the flow properties of pharmaceutical powders and blends used in solid oral dosage forms which are important consideration during dosage form development. They adapted vibratory feeder method which is a flow measurement technique that quantifies avalanche flow that used for

measurement of the flow properties of common pharmaceutical powders used in solid oral dosage forms. They measured 17 different powders with the instrument and results are described as a powder flow index (PFI). They found the PFI tendency of the powders show a relationship with flow properties. They also measured the flow property with a commercially available avalanche instrument, the Aero-Flow™, and the results were detailed as the mean time to avalanche (MTA). in view of the fact that the two instruments analyze the avalanche by different algorithms, the results were compared with nonparametric statistical evaluation of ranked data. Finally they recommended a procedure for measurement of powder flow with the vibratory feeder.

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

Again in the same year, 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.

In the same year 2004, Jonat along with his research group (Jonat et al., 2004) studied the glidant properties of compacted hydrophilic and hydrophobic colloidal silicon dioxides and compared with respect to mixing time and mixer type using microcrystalline cellulose, pregelatinized starch and α-lactose-monohydrate as model excipients. They also performed flowability studies, including angle of repose measurements and a novel dynamic conveyor belt method and found differences in the flow enhancement between the colloidal silicon dioxide types. They found that an influence of mixing conditions on flowability was hydrophilic colloidal silicon dioxide. They identified the influence of size and distribution of the colloidal silicon dioxide particles on the surface of the excipient, mixing time, mixer type. In addition, they found after moisture studies that colloidal silicon dioxide protects the excipients against a flowability decrease caused by humidity.

Again in the same year 2004, Jonat along with his research group (Jonat et al., 2004) studied the glidant properties of compacted hydrophilic and hydrophobic colloidal silicon dioxides and compared with respect to mixing time and mixer type using microcrystalline cellulose, pregelatinized starch and α-lactose-monohydrate as model excipients. They also performed flowability studies, including angle of repose measurements and a novel dynamic conveyor belt method and found differences in the flow enhancement between the colloidal silicon dioxide types. They found that an influence of mixing conditions on flowability was hydrophilic colloidal silicon dioxide. They identified the influence of size and distribution of the colloidal silicon dioxide particles on the surface of the excipient, mixing time, mixer type. In addition, they found after moisture studies that colloidal silicon dioxide protects the excipients against a flowability decrease caused by humidity. diameter and particle size, followed by the bulk density, the difference between bulk and tapped densities and the particle convexity.

In the next year 2005, Kim and his research fellows studied on the surface composition of four industrial spray-dried dairy powders, skim milk powder, whole milk powder, cream powder and whey protein concentrate by electron spectroscopy for chemical analysis (ESCA). They also studied its influence on powder flowability. They found that skim milk powder flows well compared to the other powders because the surface is made of lactose and protein with a small amount of fat, whereas the high surface fat composition inhibits the flow of whole milk, cream

and whey protein powders. They identified poor flowability of the powders with high surface fat coverage was drastically improved by removal of fat present on the surface through a brief wash with petroleum ether. Finally they concluded that even though there are several parameters including particle size, which influence the flowability of powders, the flowability of powders is powerfully influenced by the surface composition of powders, chiefly for fat-containing powders. (Kim, Chen, Pearce, 2005)

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

Then two years later, in the year 2007, Jacob and his research fellows conducted a study on flow property of co-processed particles of microcrystalline cellulose (MCC) and mannitol. They fabricated both the excipients by spray drying process to be used as a direct compression excipient in fast dissolving tablet formulation. They examined composite particles for their powder and compression properties. They observed that that an increase in the MCC proportion imparted greater compressibility to the composite particles, but the flowability of these mixtures was decreased. MCC and mannitol 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. (Jacob et al., 2007)

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

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

In the same year, 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.

In early of the next year 2009, Emery and his co research workers worked on the effect of moisture content on four pharmaceutical powders, an active pharmaceutical ingredient (API), Aspartame, Hydroxypropyl Methylcellulose (HPMC), and Respitose. They found the API and

Respitose powders were nonhygroscopic. They measured the flow property using the Jenike shear index, the Hausner's Ratio, the Carr Index, and the static and dynamic angles of repose. Finally they found that flowability of Aspartame improved with an increase in moisture content, which is credited to the formation of large, round agglomerates as well as the flowability of HPMC decreased with a raise in moisture content, recognized to the increasing strength of liquid bridges. (Emery et al., 2009)

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

In the same year, 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.

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

Most recently in the year 2013, 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.

In the same year 2013, triana and other five researcher from Belgium carried out measurements of compressibility on five granular materials: those are two different powders, hydrated lime Ca(OH)2, yttrium stabilized zirconia balls and polystyrene balls. Here, additional air volume was added to the optimal granular packing. They found that if the powder is cohesive, it traps more air compared to the non cohesive or free flowing powder which traps very smaal amount of air in static state and this free flowing powder improves the speed of packaging. (traina et al., 2013)

Again in the same year 2013, Silva and Splendor evaluated bulk density and tapped density of commonly used excipients accoding to European Pharmacopeia monograph in order to study the influence of the procedure conditions. The results suggested that leveling of the powder inside the cylinder ought to be avoided (Silva and Splendor, 2013).

In the same year 2013, Crouter and Briens, examined the effect of moisture content on flowability of six pharmaceutical powders (microcrystalline cellulose (MCC), hydroxypropyl methylcellulose (HPMC), carboxymethyl cellulose (CMC), polyvinylpyrrolidone (PVP), corn starch, and potato starch). Powder flowability was measured using established static techniques and emerging dynamic avalanche behavior measurements. Static techniques did not provide enough resolution to clearly identify changes in flowability due to increasing powder moisture content. They found that its standard deviation showed that flowability of MCC, CMC, PVP, and potato starch decreased after a critical moisture content, flowability of corn starch increased and flowability did not significantly change for HPMC. (Crouter and Briens, 2013)

CHAPTER 3

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

Name of Excipients	Source (Supplier Name)
Starch	MERK, Germany
Magnesium stearate	MERK, Germany
Carboxymethylcellulose	MERK, Germany
Polyethylene glycol	MERK, Germany
talc	MERK, Germany

3.1.3 Apparatus:

Table 3.2: Some apparatus are listed in the following table those were used through the research work.

Serial No.	Apparatus
1.	Beaker
2.	Test Tubes
3.	Aluminium Foil Paper

4.	Cling Wrap
5.	Mortar & Pastels
6.	Spatula
7.	Funnel
8.	Measuring Cylinder
9.	Conical Flask
10.	White Paper
11.	Black Marker
12.	Scale

3.2 METHODS:

3.2.1 Preparation of various set of formulas:

Several formulas of a combination of excipients which includes diluents, lubricants, disintegrants and binders 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, F4 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 (anti adherent):

After that, a 3g sample was made through calculating the required amount of the formula with the selected anti adherent. Anti adherent was 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 anti adherent, five different mixtures of 3g each were arranged and settled in five 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= $\frac{100(V_o - V_f)}{V_o}$.

$$\text{Hausner ratio} = \frac{V_0}{V_f}$$

Where,

Vo = Bulk volume

Vf = 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 3g 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.

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

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.

Table 3.3: The following amounts of excipients (given with their use) were taken for the preparation of Formula 1 (F1)-15g

Ingredients Name	Purpose of Use	Percentage Quantity	Amount in 15g
Starch	Diluents	40%	6
Polyethylene glycol	Binder	25%	3.75
Carboxymethylecellulose	Disintegrant	10%	3
Talc	Lubricant	15%	2.25
		Total=100%	Total=15g

After preparing 15g of F1, specific anti adherent was mixed with it in different fixed and justified ratio. For this formula, magnesium stearate was used. The required amount of both magnesium stearate and F1 was calculated for preparing each 3g of mixture in five different ratios. A total of four sets of sample mixture of 3g were set up for further procedure that is the determination of flow property.

Table 3.4: The amount of magnesium stearate and F1 in different ratio in 3g

Ratio	Mg stearate: F1	Amount of mg stearate: F1 (in g)
1	10% : 90%	0.3 : 2.7
2	15% : 95%	0.45 : 2.55
3	17% : 83%	0.51 : 2.49
4	20% : 80%	0.6 : 2.4
5	22% : 78%	0.66 : 2.34

3.2.4.2 Preparation of Formula 2 (F2):

By choosing different excipients except anti adherent, 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.

Table 3.5: 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
Starch	Diluents	40%	8
Polyethylene glycol	Binder	25%	5
Carboxymethylecellulose	Disintegrant	20%	4
Talc	Lubricant	15%	3
		Total=100%	Total=20g

After preparing 20g of F2, specific anti adherent were mixed with it in different fixed and justified ratio. For this formula, magnesium stearate was used. The required amount of both magnesium stearate and F2 was calculated for preparing each 3g of mixture in five different ratios.

A total of four sets of sample mixture of 3g were set up for further procedure that is the determination of flow property.

Table 3.6: The amount of magnesium stearate and F2 in different ratio in 3g

Ratio	Mg stearate: F2	Amount of mg stearate: F2 (in g)
1	7% : 93%	0.21 : 2.79
2	8% : 92%	0.24 : 2.76
3	9% : 91%	0.27 : 2.73
4	10% : 90%	0.3 : 2.7
5	11% : 89%	0.33 : 2.6

3.2.4.3 Preparation of Formula 3 (F3):

By choosing different excipients except anti adherent, 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.

Table 3.7: The following amounts of excipients (given with their use) were taken for the preparation of Formula 3 (F3)-15g

Ingredients Name	Purpose of Use	Percentage Quantity	Amount in 15g
Starch	Diluents	50%	7.5
Polyethylene glycol	Binder	15%	2.25
Carboxymethylecellulose	Disintegrant	20%	3
Talc	Lubricant	15%	2.25
		Total=100%	Total=15g

After preparing 15g of F3, specific anti adherent was mixed with it in different fixed and justified ratio. For this formula, magnesium stearate was used. The required amount of both magnesium stearate and F3 was calculated for preparing each 3g of mixture in five different ratios. A total of four sets of sample mixture of 3g were set up for further procedure that is the determination of flow property.

Table 3.8: The amount of starch and F3 in different ratio in 3g

Ratio	Mg stearate: F3	Amount of mg stearate: F3 (in g)
1	6% : 94%	0.18 : 2.82
2	7% : 93%	0.21 : 2.79
3	8% : 92%	0.24 : 2.76
4	11% : 89%	0.33 : 2.67
5	12% : 88%	0.36 : 2.64

3.2.4.4 Preparation of Formula 4 (F4):

By choosing different excipients except anti adherent, 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.

Table 3.9: The following amounts of excipients (given with their use) were taken for the preparation of Formula 4 (F4)-15g

Ingredients Name	Purpose of Use	Percentage Quantity	Amount in 15g
Starch	Diluents	50%	7.5
Polyethylene glycol	Binder	25%	2.5
Carboxymethylecellulose	Disintegrant	20%	2
Talc	Lubricant	15%	1.5
		Total=100%	Total=15g

After preparing 15g of F4, specific anti adherent was mixed with it in different fixed and justified ratio. For this formula, magnesium stearate was used. The required amount of both magnesium stearate and F4 was calculated for preparing each 3g of mixture in five different ratios. A total of four sets of sample mixture of 3g were set up for further procedure that is the determination of flow property.

Table 3.10: The amount of calcium phosphate and F4 in different ratio in 3g

Ratio	Mg stearate: F4	Amount of mg stearate: F4 (in g)
1	6.5% : 93.5%	0.19 : 2.80
2	7.5% : 92.5%	0.22 : 2.76
3	8.5% : 91.5%	0.25 : 2.75
4	9.5% : 90.5%	0.28 : 2.72
5	10.5% : 89.5%	0.315 : 2.69

After that, active ingredients (amlodipine and propranolol) were mixed with the mixture. From five set of ratio 1 gm of mixture was taken. After that it was mixed with 0.0625gm of active ingredient and flow property of all the mixtures were measured.

Chapter 4

Result

4.1 Calculation of flow property of the prepared mixture ratio of anti adherent and formulas:

4.1.1 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 five times and the average value was taken. The observed value is given below:

Table 4.1: Calculation of Carr's index and Hausner ratio for set-1

Ratio	Bulk volume(ml)	Highest bulk volume(ml)	Tapped volume(ml)	Lowest tapped volume(ml)	Hausner ratio	Carr's index
Ratio 1	8.5	9	6.5	6.5	1.38	27.77
	9		7			
	8.5		6.5			
	8		7			
	9		7			
Ratio 2	9	9	6.7	6.7	1.35	25.55
	8.7		6.8			
	8.5		6.8			
	8.9		7			
	9		7			
Ratio 3	8.5	8.5	6.4	6.4	1.33	24.70
	8		6.8			
	8.4		6.5			
	8.2		6.5			
	8		6.8			

Ratio 4	8.5	8.5	6.7	6.5	1.31	23.52
	7.9		6.8			
	7.8		6.8			
	7.9		6.5			
	8		6.5			
Ratio 5	8	8	6.2	6.2	1.29	22.5
	7.9		6.1			
	7.8		6			
	8		6			
	8		6.2			

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

Table 4.2: Calculation of Angle of repose for set-1

Ratio	Height (h) (cm)	Avg height (h) (cm)	Diameter (2r) (cm)	Avg diameter (2r) (cm)	Radius (r) (cm)	Angle of repose
Ratio 1	2.4	2.46	4.98	5.02	2.50	44.45°
	2.5		4.94			
	2.4		4.9			
	2.45		5			
	2.55		5.26			
Ratio 2	2.4	2.38	5.04	4.96	2.48	43.84°
	2.38		5.02			
	2.42		4.88			
	2.35		4.9			
	2.36		4.96			
Ratio 3	2.35		5.2			

	2.38	2.356	5.2	5.10	2.55	42.7°
	2.3		4.84			
	2.35		5.14			
	2.4		5.16			
Ratio 4	2.3	2.31	5.06	5.18	2.59	41.70°
	2.35		5.22			
	2.3		5.14			
	2.35		5.22			
	2.25		5.28			
Ratio 5	2.2	2.24	5.32	5.26	2.63	40.52°
	2.25		5.22			
	2.25		5.34			
	2.28		5.28			
	2.2		5.12			

4.1.2. 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 five times and the average value was taken. The observed value is given below:

Table 4.3: Calculation of Carr's index and Hausner ratio for set-2

Ratio	Bulk volume (ml)	Highest bulk volume(ml)	Tapped volume (ml)	Lowest tapped volume (ml)	Hausner ratio	Carr's index
Ratio 1	8.5	8.5	6.7	6.6	1.27	22.35
	8		6.6			
	8.3		6.8			

	8.5		6.6			
	8		6.6			
Ratio 2	8	8.5	6.8	6.8	1.25	22.35
	7.9		7			
	7.8		6.8			
	8		6.9			
	8		7			
Ratio 3	8	8	6.6	6.55	1.22	18.12
	7.8		6.7			
	8		6.55			
	7.8		6.8			
	7.7		6.8			
Ratio 4	8	8	6.7	6.7	1.19	16.25
	7.8		6.8			
	7.5		7			
	8		7			
	7.5		6.8			
Ratio 5	8	8	6.8	6.8	1.17	15
	8		6.8			
	7.8		6.9			
	7.8		7			
	7.5		6.8			

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

Table 4.4: Calculation of Angle of repose for set-2

Ratio	Height (h) (cm)	Avg height (h) (cm)	Diameter (2r) (cm)	Avg diameter (2r) (cm)	Radius (r) (cm)	Angle of repose
Ratio 1	1.6	1.54	4.96	4.792	2.396	32.72°
	1.5		4.7			
	1.5		4.62			
	1.6		4.98			
	1.5		4.7			
Ratio 2	1.4	1.5	4.74	4.88	2.44	31.56°
	1.5		4.84			
	1.5		4.82			
	1.6		5.18			
	1.5		4.82			
Ratio 3	1.4	1.5	4.64	4.90	2.45	31.10°
	1.5		5			
	1.4		4.62			
	1.6		5.26			
	1.5		5			
Ratio 4	1.5	1.46	5	4.88	2.44	30.88°
	1.4		4.68			
	1.5		4.72			
	1.4		5			
	1.5		5			
Ratio 5	1.4	1.44	4.88	5.03	2.52	29.77°
	1.5		5.22			
	1.4		4.9			
	1.5		5.22			
	1.4		4.94			

4.1.3 For set 3:

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

Table 4.5: Calculation of Carr's index and Hausner ratio for set-3

Ratio	Bulk volume (ml)	Highest bulk volume(ml)	Tapped volume(ml)	Lowest tapped volume(ml)	Hausner ratio	Carr's index
Ratio 1	9	9	7	7	1.28	22.22
	9		7			
	8		7.1			
	8.5		6.8			
	9		7.2			
Ratio 2	8	8.8	7	7	1.26	20.45
	8.5		7			
	8.5		7.5			
	8.8		7.2			
	8		7			
Ratio 3	8	8.5	6.8	6.8	1.25	20
	8.5		7			
	8.5		7			
	8.2		7.2			
	8		6.8			
Ratio 4	9	9	7.5	7.3	1.23	18.88
	8.5		7.3			
	8		7.5			
	8.8		7.5			
	8		7.5			

Ratio 5	8	9	7.7	7.5	1.20	16.66
	8		7.5			
	8.5		7.5			
	9		7.5			
	8.1		7.8			

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

Table 4.6: Calculation of Angle of repose for set-3

Ratio	Height (h) (cm)	Avg height (h) (cm)	Diameter (2r) (cm)	Avg diameter (2r) (cm)	Radius (r) (cm)	Angle of repose
Ratio 1	1.6	1.56	3.5	3.66	1.83	40.41°
	1.5		3.76			
	1.5		3.52			
	1.6		3.76			
	1.6		3.76			
Ratio 2	1.6	1.55	3.7	3.77	1.88	39.55°
	1.5		3.66			
	1.5		3.86			
	1.6		3.84			
	1.58		3.82			
Ratio 3	1.6	1.58	3.8	3.98	1.99	38.44°
	1.5		4.02			
	1.58		4.06			
	1.6		4.02			
	1.62		4			

Ratio 4	1.58	1.46	4.2	4.13	2.06	37.57°
	1.6		3.8			
	1.5		4.2			
	1.62		4.2			
	1.6		4.24			
Ratio 5	1.6	1.58	4.88	5.03	2.52	35.21°
	1.5		5.22			
	1.6		4.9			
	1.58		5.22			
	1.62		4.94			

4.1.4 For set 4:

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

Table 4.7: Calculation of Carr's index and Hausner ratio for set-4

Ratio	Bulk volume (ml)	Highest bulk volume(ml)	Tapped volume(ml)	Lowest tapped volume(ml)	Hausner ratio	Carr's index
Ratio 1	8.5	8.5	6.7	6.5	1.30	23.52
	8		6.8			
	8.2		6.8			
	8		7			
	7.8		6.8			
Ratio 2	8.5	9	7.5	7	1.28	22.22
	8.5		7.2			
	9		7.5			
	8.2		7.1			

	9		7			
Ratio 3	8.5	8.5	6.7	6.7	1.27	21.17
	8.5		7.5			
	8.5		7.2			
	8		7			
	7.8		6.8			
Ratio 4	8	8.2	6.5	6.5	1.26	20.73
	7.8		6.8			
	7.5		7			
	8.2		7.1			
	8		6.5			
Ratio 5	8	8	6.5	6.5	1.23	18.75
	8		6.8			
	7.8		6.5			
	7.8		7			
	7.5		6.8			

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

Table 4.8: Calculation of Angle of repose for set-4

Ratio	Height (h) (cm)	Avg height (h) (cm)	Diameter (2r) (cm)	Avg diameter (2r) (cm)	Radius (r) (cm)	Angle of repose
Ratio 1	1.6	1.56	4.36	4.31	2.16	35.89°
	1.5		4.34			
	1.5		4.3			
	1.6		4.24			
	1.6		4.32			
Ratio 2	1.6	1.58	4.48	4.50	2.25	35.19°
	1.5		4.72			
	1.5		4.56			
	1.6		4.4			
	1.7		4.36			
Ratio 3	1.6	1.56	4.6	4.59	2.29	34.20°
	1.5		4.54			
	1.5		4.58			
	1.6		4.6			
	1.6		4.62			
Ratio 4	1.5	1.54	4.8	4.70	2.35	33.26°
	1.6		4.62			
	1.5		4.48			
	1.5		4.78			
	1.6		4.8			
Ratio 5	1.5	1.47	4.8	4.7	2.35	31.85°
	1.5		4.52			
	1.4		4.62			
	1.5		4.74			
	1.4		4.82			

4.2. Calculation of flow property of the amlodipine and formulas:

4.2.1 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:

Table 4.9: Calculation of Carr's index and Hausner ratio for set-1

Ratio	Bulk volume (ml)	Highest bulk volume(ml)	Tapped volume (ml)	Lowest tapped volume(ml)	Hausner ratio	Carr's index
Ratio 1	4.1	4.1	3	3	1.36	26.83
	4		3.2			
	3.8		3			
	3.9		3.1			
	4.1		3.2			
Ratio 2	4.3	4.3	3.2	3.2	1.34	25.58
	4.2		3.3			
	4		3.2			
	4.3		3.3			
	4.1		3.2			
Ratio 3	4.1	4.1	3.1	3.1	1.32	24.39
	4		3.2			
	4.1		3.1			
	3.9		3.1			
	3.8		3.2			

Ratio 4	4.3	4.3	3.3	3.3	1.30	23.25
	4.2		3.4			
	4		3.5			
	4.1		3.3			
	4.3		3.4			
Ratio 5	4.1	4.1	3.2	3.2	1.28	21.95
	4		3.3			
	4.4		3.2			
	3.9		3.3			
	3.8		3.4			

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

Table 4.10: Calculation of Angle of repose for set-1

Ratio	Height (h) (cm)	Avg height (h) (cm)	Diameter (2r) (cm)	Avg diameter (2r) (cm)	Radius (r) (cm)	Angle of repose
Ratio 1	1.35	1.31	2.9	2.84	1.42	42.64°
	1.3		2.82			
	1.35		2.92			
	1.3		2.84			
	1.25		2.74			
Ratio 2	1.3	1.31	2.92	2.96	1.48	41.55°
	1.35		3.06			
	1.25		2.78			
	1.3		2.94			
	1.35		3.08			

Ratio 3	1.45	1.46	3.4	3.39	1.69	40.96°
	1.45		3.5			
	1.5		3.4			
	1.5		3.5			
	1.4		3.14			
Ratio 4	1.4	1.39	3.44	3.34	1.67	39.76°
	1.4		3.34			
	1.45		3.38			
	1.35		3.3			
	1.35		3.24			
Ratio 5	1.35	1.33	3.38	3.35	1.68	38.38°
	1.30		3.3			
	1.34		3.38			
	1.35		3.38			
	1.30		3.32			

4.2.2 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 five times and the average value was taken. The observed value is given below:

Table 4.11: Calculation of Carr's index and Hausner ratio for set-2

Ratio	Bulk volume(ml)	Highest bulk volume(ml)	Tapped volume(ml)	Lowest tapped volume(ml)	Hausner ratio	Carr's index
Ratio 1	4	4.5	3.5	3.5	1.28	22.22
	4.5		3.8			
	4.2		3.5			
	4.1		3.6			
	4		3.5			
Ratio 2	4.5	4.5	3.7	3.5	1.25	20
	4		3.6			
	4.5		3.8			
	4.3		3.6			
	4.2		3.7			
Ratio 3	4	4.3	3.5	3.5	1.23	18.60
	4.1		3.5			
	4		3.6			
	4.3		3.5			
	4.1		3.6			
Ratio 4	4	4.2	3.5	3.5	1.2	16.66
	4.2		3.7			
	4		3.6			
	4.1		3.5			
	4		3.8			
Ratio 5	4	4.1	3.5	3.5	1.17	14.63
	4.1		3.8			
	4.1		3.5			
	4		3.5			
	4		3.5			

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

Table 4.12: Calculation of Angle of repose for set-2

Ratio	Height (h) (cm)	Avg height (h) (cm)	Diameter (2r) (cm)	Avg diameter (2r) (cm)	Radius (r) (cm)	Angle of repose
Ratio 1	1.1	1.04	3.2	3.31	1.65	32.15
	1		3.5			
	1		3.24			
	1.1		3.48			
	1		3.12			
Ratio 2	0.9	0.96	2.9	3.07	1.54	31.92
	0.8		2.58			
	1		3.18			
	1.1		3.5			
	1		3.2			
Ratio 3	0.9	1	3.14	3.29	1.65	31.22
	0.9		3.1			
	1.1		3.54			
	1		3.18			
	1.1		3.5			
Ratio 4	1	0.98	3.46	3.32	1.66	30.56
	0.9		3.04			
	1.1		3.54			
	1		3.44			
	0.9		3.1			
Ratio 5	0.9	0.96	3.48	3.45	1.72	29.18
	1		3.42			

	1		3.38			
	0.9		3.46			
	1		3.44			

4.2.3 For set 3:

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

Table 4.13: Calculation of Carr's index and Hausner ratio for set-3

Ratio	Bulk volume(ml)	Highest bulk volume(ml)	Tapped volume(ml)	Lowest tapped volume(ml)	Hausner ratio	Carr's index
Ratio 1	4.1	4.3	3.8	3.3	1.30	23.25
	4.3		3.5			
	4		3.3			
	3.8		3.3			
	4		3.5			
Ratio 2	4.1	4.2	3.5	3.3	1.27	21.43
	4.2		3.3			
	4		3.4			
	4.2		3.4			
	4.1		3.5			
Ratio 3	4.2	4.2	3.5	3.4	1.23	19.04
	4.1		3.6			
	4		3.5			
	4		3.4			
	4		3.5			

Ratio 4	4.1	4.1	3.6	3.4	1.20	17.07
	4		3.5			
	4.1		3.6			
	4.1		3.4			
	4		3.5			
Ratio 5	4.3	4.3	3.8	3.6	1.19	16.27
	4.2		3.6			
	4.1		3.7			
	4		3.7			
	4		3.6			

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

Table 4.14: Calculation of Angle of repose for set-3

Ratio	Height (h) (cm)	Avg height (h) (cm)	Diameter (2r) (cm)	Avg diameter (2r) (cm)	Radius (r) (cm)	Angle of repose
Ratio 1	1.45	1.46	3.4	3.36	1.68	40.96
	1.5		3.38			
	1.5		3.4			
	1.4		3.5			
	1.45		3.14			
Ratio 2	1.4	1.39	3.44	3.34	1.67	39.76
	1.4		3.34			
	1.45		3.38			
	1.35		3.3			
	1.35		3.24			

Ratio 3	1.35	1.33	3.38	3.35	1.68	38.38
	1.30		3.3			
	1.34		3.38			
	1.35		3.38			
	1.30		3.32			
Ratio 4	1.3	1.25	3.36	3.27	1.63	37.40
	1.25		3.3			
	1.2		3.16			
	1.3		3.36			
	1.2		3.16			
Ratio 5	1.1	1.15	3.24	3.14	1.57	36.24
	1.2		3.02			
	1.1		3.24			
	1.15		3.2			
	1.2		3.02			

4.2.4 For set 4:

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

Table 4.15: Calculation of Carr's index and Hausner ratio for set-4

Ratio	Bulk volume(ml)	Highest bulk volume(ml)	Tapped volume(ml)	Lowest tapped volume(ml)	Hausner ratio	Carr's index
Ratio 1	4	4.1	3.15	3.15	1.30	23.17
	4.1		3.2			
	3.9		3.3			
	3.8		3.2			
	4.1		3.15			
Ratio 2	4.2	4.2	3.3	3.3	1.27	21.43
	4.1		3.4			
	4		3.3			
	4		3.4			
	3.9		3.3			
Ratio 3	4.3	4.3	3.4	3.4	1.26	20.93
	4.2		3.5			
	4		3.4			
	4.1		3.5			
	4.3		3.5			
Ratio 4	4.1	4.1	3.3	3.3	1.24	19.51
	4		3.4			
	4.1		3.4			
	3.9		3.3			
	4		3.5			
Ratio 5	4.3	4.3	3.8	3.5	1.22	18.60
	4		3.5			
	4.1		3.6			
	4.2		3.5			
	4.3		3.6			

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

Table 4.16: Calculation of Angle of repose for set-4

Ratio	Height (h) (cm)	Avg height (h) (cm)	Diameter (2r) (cm)	Avg diameter (2r) (cm)	Radius (r) (cm)	Angle of repose
Ratio 1	1.4	1.36	3.96	3.82	1.91	35.47
	1.4		3.92			
	1.4		3.86			
	1.3		3.68			
	1.3		3.66			
Ratio 2	1.3	1.25	3.8	3.65	1.83	34.36
	1.2		3.54			
	1.3		3.8			
	1.2		3.52			
	1.25		3.6			
Ratio 3	1.2	1.19	3.6	3.55	1.78	33.23
	1.15		3.54			
	1.1		3.38			
	1.2		3.56			
	1.2		3.68			
Ratio 4	1.1	1.15	3.4	3.58	1.79	32.71
	1.15		3.58			
	1.1		3.42			
	1.2		3.74			
	1.2		3.76			
Ratio 5	1	1.03	3.3	3.37	1.68	31.42
	0.9		2.96			

	1		3.32			
	1.15		3.7			
	1.1		3.56			

4.3 Calculation of flow property of the propranolol and formulas:

4.3.1 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:

Table 4.17: Calculation of Carr's index and Hausner ratio for set-1

Ratio	Bulk volume(ml)	Highest bulk volume(ml)	Tapped volume(ml)	Lowest tapped volume(ml)	Hausner ratio	Carr's index
Ratio 1	4.3	4.3	3.2	3.2	1.34	25.58
	4.1		3.3			
	4.3		3.2			
	4		3.3			
	4		3.2			
Ratio 2	4.1	4.1	3.1	3.1	1.32	24.39
	4		3.2			
	4.1		3.1			
	4		3.1			
	3.9		3.2			

Ratio 3	4.3	4.3	3.3	3.3	1.30	23.25
	4.1		3.4			
	4.3		3.4			
	4.1		3.3			
	4.2		3.5			
Ratio 4	4.1	4.1	3.3	3.2	1.28	21.95
	4		3.2			
	4		3.2			
	4.1		3.3			
	4		3.3			
Ratio 5	4	4	3.2	3.2	1.25	20
	4		3.3			
	4		3.2			
	3.9		3.3			
	3.9		3.2			

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

Table 4.18: Calculation of Angle of repose for set-1

Ratio	Height (h) (cm)	Avg height (h) (cm)	Diameter (2r) (cm)	Avg diameter (2r) (cm)	Radius (r) (cm)	Angle of repose
Ratio 1	1.3	1.31	2.92	2.96	1.48	41.55°
	1.35		3.06			
	1.25		2.78			
	1.3		2.94			
	1.35		3.08			

Ratio 2	1.45	1.46	3.4	3.37	1.68	40.96°
	1.45		3.4			
	1.5		3.4			
	1.5		3.14			
	1.4		3.5			
Ratio 3	1.4	1.39	3.34	3.32	1.66	39.76°
	1.4		3.34			
	1.35		3.38			
	1.35		3.3			
	1.45		3.24			
Ratio 4	1.30	1.33	3.38	3.35	1.68	38.38°
	1.35		3.3			
	1.30		3.38			
	1.35		3.38			
	1.34		3.32			
Ratio 5	1.3	1.31	3.3	3.36	1.68	37.73°
	1.3		3.4			
	1.32		3.3			
	1.32		3.4			
	1.33		3.42			

4.3.2 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 five times and the average value was taken. The observed value is given below:

Table 4.19: Calculation of Carr's index and Hausner ratio for set-2

Ratio	Bulk volume(ml)	Highest bulk volume(ml)	Tapped volume(ml)	Lowest tapped volume(ml)	Hausner ratio	Carr's index
Ratio 1	4.4	4.4	3.4	3.4	1.29	22.73
	4.3		3.5			
	4.4		3.5			
	4		3.4			
	4.4		3.4			
Ratio 2	4.4	4.4	3.5	3.5	1.26	20.45
	4.3		3.6			
	4.2		3.5			
	4.4		3.6			
	4.2		3.5			
Ratio 3	4.5	4.5	3.6	3.6	1.25	20
	4.5		3.6			
	4.4		3.7			
	4.4		3.7			
	4.3		3.8			
Ratio 4	4	4.3	3.5	3.5	1.23	18
	4		3.6			
	4.3		3.5			
	4.3		3.6			
	4.2		3.5			
Ratio 5	4.2	4.2	3.6	3.5	1.20	16.66
	4		3.5			
	4.2		3.6			
	4.2		3.5			
	4		3.6			

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

Table 4.20: Calculation of Angle of repose for set-2

Ratio	Height (h) (cm)	Avg height (h) (cm)	Diameter (2r) (cm)	Avg diameter (2r) (cm)	Radius (r) (cm)	Angle of repose
Ratio 1	0.9	0.96	2.9	3.07	1.54	31.92°
	0.8		2.58			
	1		3.18			
	1.1		3.5			
	1		3.2			
Ratio 2	1	0.98	3.44	3.31	1.66	30.56°
	0.9		3.04			
	1.1		3.44			
	1		3.54			
	0.9		3.1			
Ratio 3	1	0.96	3.48	3.44	1.72	29.18°
	1		3.42			
	0.9		3.38			
	1		3.46			
	0.9		3.44			
Ratio 4	1	0.96	3.7	3.57	1.79	28.25°
	1		3.74			
	0.9		3.38			
	1		3.32			
	0.9		3.72			
Ratio 5	1	0.88	3.06	3.36	1.68	27.66°
	0.8		3.08			

	0.8		3.44			
	0.9		3.4			
	0.9		3.8			

4.3.3 For set 3:

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

Table 4.21: Calculation of Carr's index and Hausner ratio for set-3

Ratio	Bulk volume(ml)	Highest bulk volume(ml)	Tapped volume(ml)	Lowest tapped volume(ml)	Hausner ratio	Carr's index
Ratio 1	4.5	4.5	3.5	3.5	1.28	22.22
	4.2		3.6			
	4.4		3.5			
	4.4		3.7			
	4.5		3.5			
Ratio 2	4.3	4.3	3.4	3.4	1.26	20.93
	4.3		3.6			
	4.2		3.5			
	4.1		3.4			
	4.2		3.5			
Ratio 3	4	4.3	3.6	3.5	1.23	18.60
	4		3.6			
	4.3		3.5			
	4.2		3.5			
	4.3		3.5			

Ratio 4	4	4.2	3.5	3.5	1.20	16.66
	4		3.6			
	4.2		3.7			
	4.1		3.6			
	4.2		3.5			
Ratio 5	4.1	4.1	3.6	3.5	1.17	14.63
	4		3.5			
	4.1		3.7			
	4.1		3.5			
	4		3.6			

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

Table 4.22: Calculation of Angle of repose for set-3

Ratio	Height (h) (cm)	Avg height (h) (cm)	Diameter (2r) (cm)	Avg diameter (2r) (cm)	Radius (r) (cm)	Angle of repose
Ratio 1	1.30	1.33	3.38	3.29	1.65	38.38°
	1.35		3.3			
	1.34		3.38			
	1.35		3.38			
	1.30		3.32			
Ratio 2	1.3	1.25	3.36	3.27	1.63	37.40°
	1.2		3.3			
	1.3		3.16			
	1.25		3.36			
	1.2		3.16			

Ratio 3	1.4	1.34	3.96	3.82	1.91	35.47°
	1.3		3.92			
	1.4		3.86			
	1.3		3.68			
	1.3		3.66			
Ratio 4	1.2	1.17	3.6	3.55	1.78	33.23°
	1.15		3.54			
	1.1		3.38			
	1.2		3.56			
	1.2		3.68			
Ratio 5	1	1.03	3.3	3.37	1.68	31.42°
	0.9		2.96			
	1		3.32			
	1.15		3.7			
	1.1		3.56			

4.3.4 For set 4:

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

Table 4.23: Calculation of Carr's index and Hausner ratio for set-4

Ratio	Bulk volume(ml)	Highest bulk volume(ml)	Tapped volume(ml)	Lowest tapped volume(ml)	Hausner ratio	Carr's index
Ratio 1	4.2	4.2	3.4	3.3	1.27	21.43
	4.1		3.3			
	4.2		3.5			
	4		3.3			
	4.1		3.4			

Ratio 2	4.4	4.5	3.6	3.6	1.25	20
	4.5		3.6			
	4.5		3.7			
	4.4		3.6			
	4.5		3.7			
Ratio 3	4.2	4.2	3.6	3.4	1.23	19.04
	4.1		3.6			
	4.2		3.4			
	4.1		3.4			
	4		3.5			
Ratio 4	4	4.1	3.5	3.4	1.20	17.07
	4		3.6			
	4.1		3.4			
	3.9		3.6			
	4.1		3.4			
Ratio 5	4.1	4.1	3.6	3.5	1.17	14.63
	4		3.5			
	4.1		3.5			
	4.1		3.5			
	4		3.6			

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

Table 4.24: Calculation of Angle of repose for set-4

Ratio	Height (h) (cm)	Avg height (h) (cm)	Diameter (2r) (cm)	Avg diameter (2r) (cm)	Radius (r) (cm)	Angle of repose
Ratio 1	1.3	1.25	3.8	3.65	1.83	34.36°
	1.2		3.54			
	1.25		3.8			
	1.3		3.52			
	1.2		3.6			
Ratio 2	1.1	1.15	3.4	3.58	1.79	32.71°
	1.2		3.42			
	1.1		3.76			
	1.2		3.74			
	1.15		3.58			
Ratio 3	1.1	1	3.14	3.29	1.65	31.22°
	1		3.1			
	1.1		3.54			
	0.9		3.18			
	0.9		3.5			
Ratio 4	0.9	0.96	3.48	3.44	1.72	29.18°
	1		3.42			
	1		3.38			
	0.9		3.46			
	1		3.46			
Ratio 5	0.8	0.88	3.08	3.36	1.68	27.66°
	0.9		3.06			
	0.8		3.4			
	0.9		3.44			
	1		3.8			

4.4. Graph section:

4.4.1 Comparison between the values of formulas, amlodipine and propranolol for set 1:

By plotting percentage ratio of mg stearate in X-axis and respected Carr's index in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, Carr's index of formulas, amlodipine and propranolol can be achieved and comparison can made.

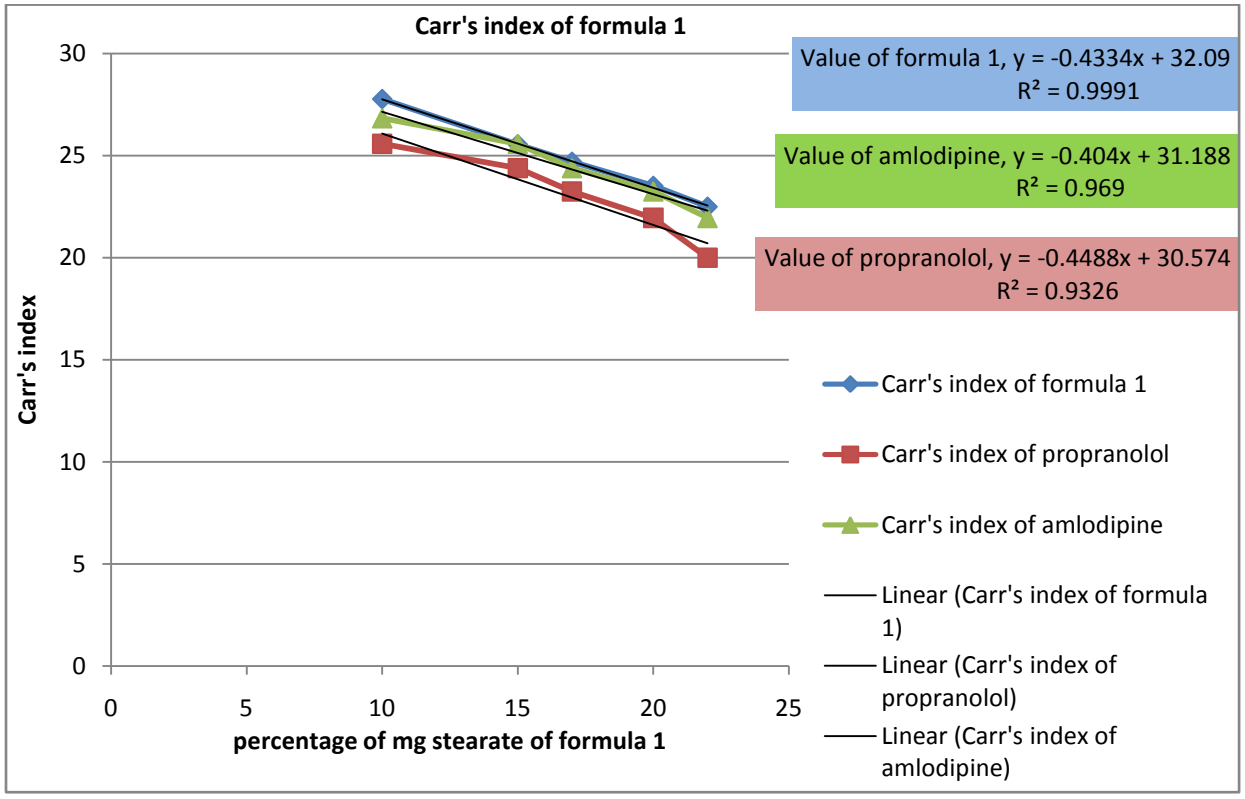

Figure 4.1: A percentage ratio of mg stearate versus Carr's index graph

By plotting percentage ratio of mg stearate in X-axis and respected Hausner ratio in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, Hausner ratio of formulas, amlodipine and propranolol can be achieved and comparison can made.

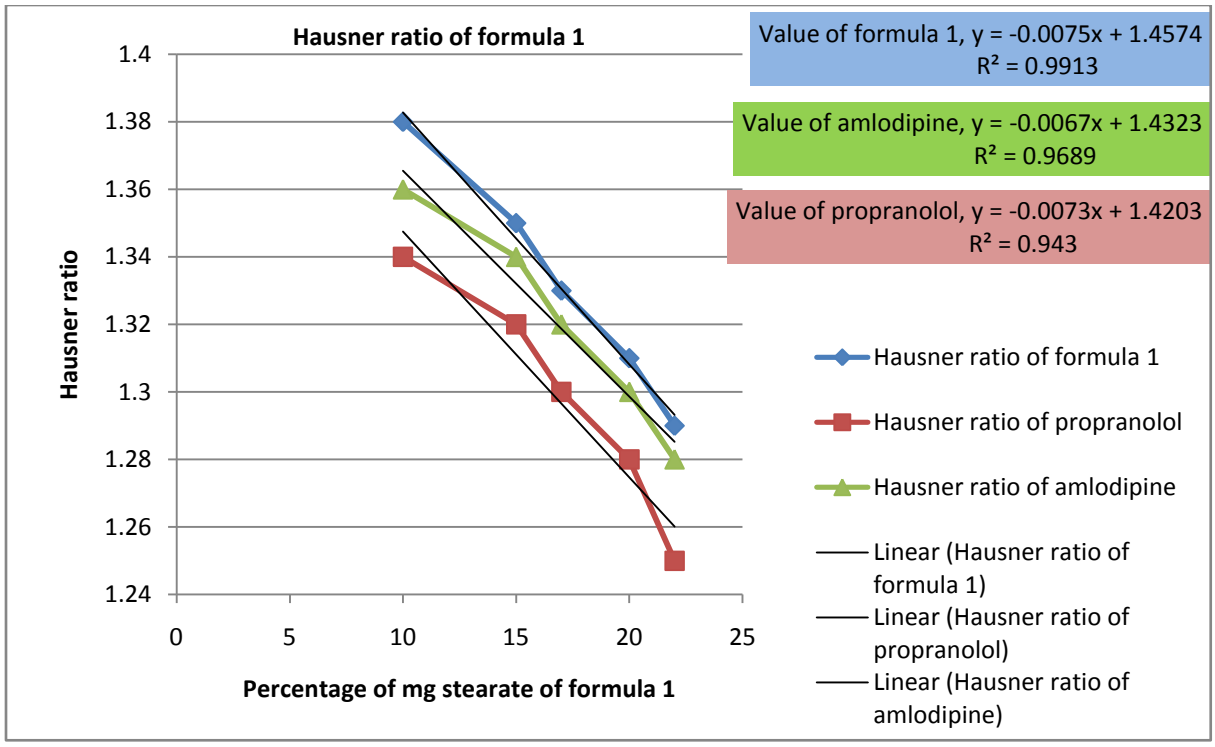

Figure 4.2: A percentage ratio of mg stearate versus Hausner ratio graph

By plotting percentage ratio of mg stearate in X-axis and respected angle of repose in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, angle of repose of formulas, amlodipine and propranolol can be achieved and comparison can made.

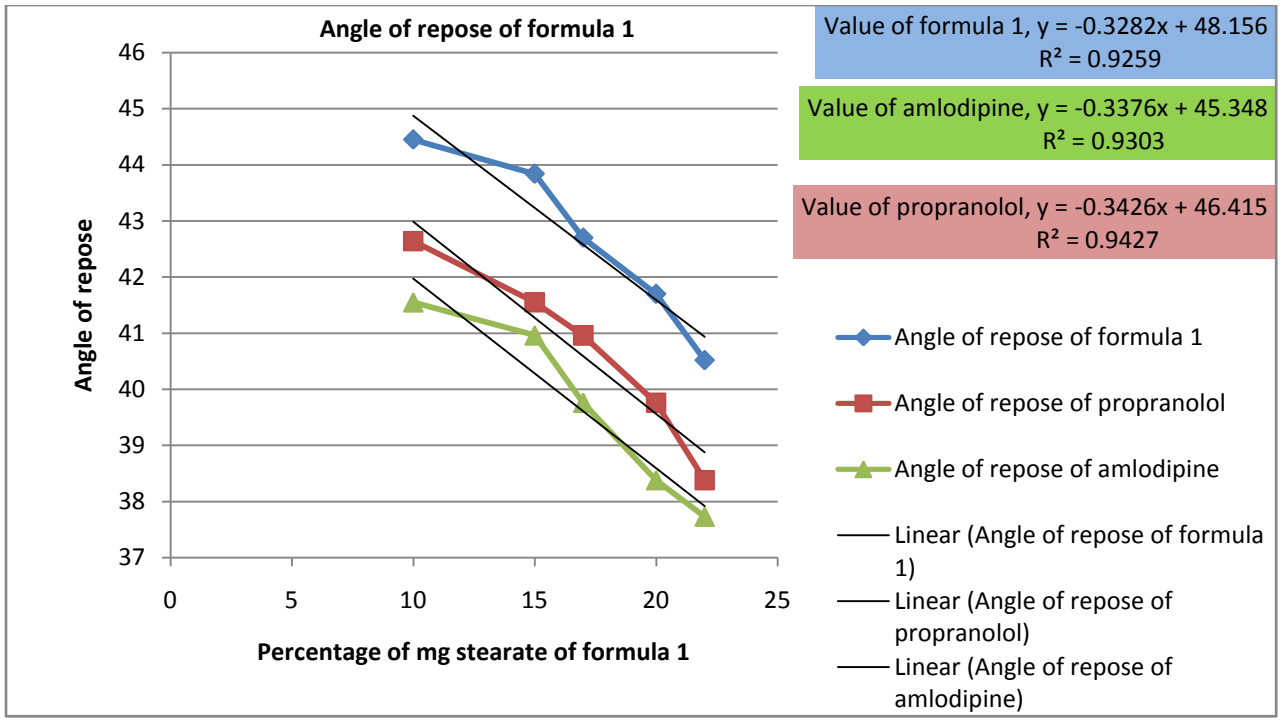

Figure 4.3: A percentage ratio of mg stearate versus angle of repose graph

4.4.2 Comparison between the values of formulas, amlodipine and propanolol for set 2:

By plotting percentage ratio of mg stearate in X-axis and respected Carr's index in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, Carr's index of formulas, amlodipine and propranolol can be achieved and comparison can made.

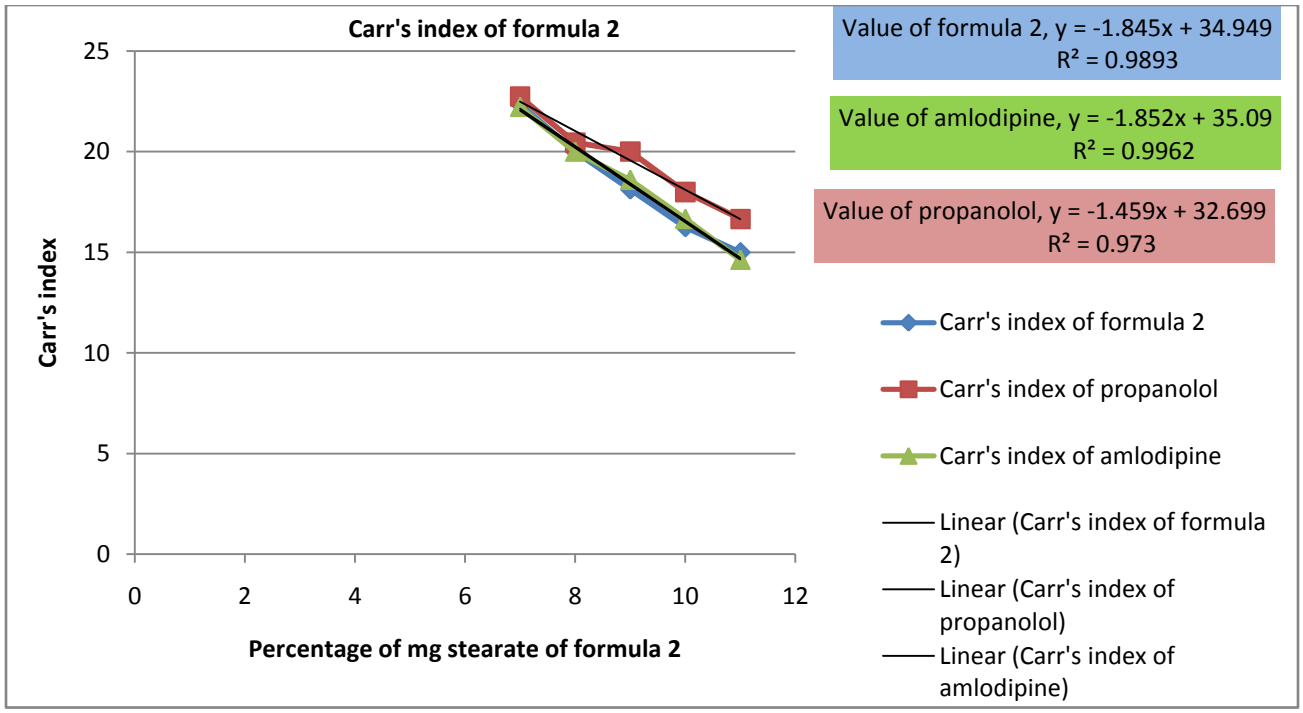

Figure 4.4: A percentage ratio of mg stearate versus Carr's index graph

By plotting percentage ratio of mg stearate in X-axis and respected Hausner ratio in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, Hausner ratio of formulas, amlodipine and propranolol can be achieved and comparison can made.

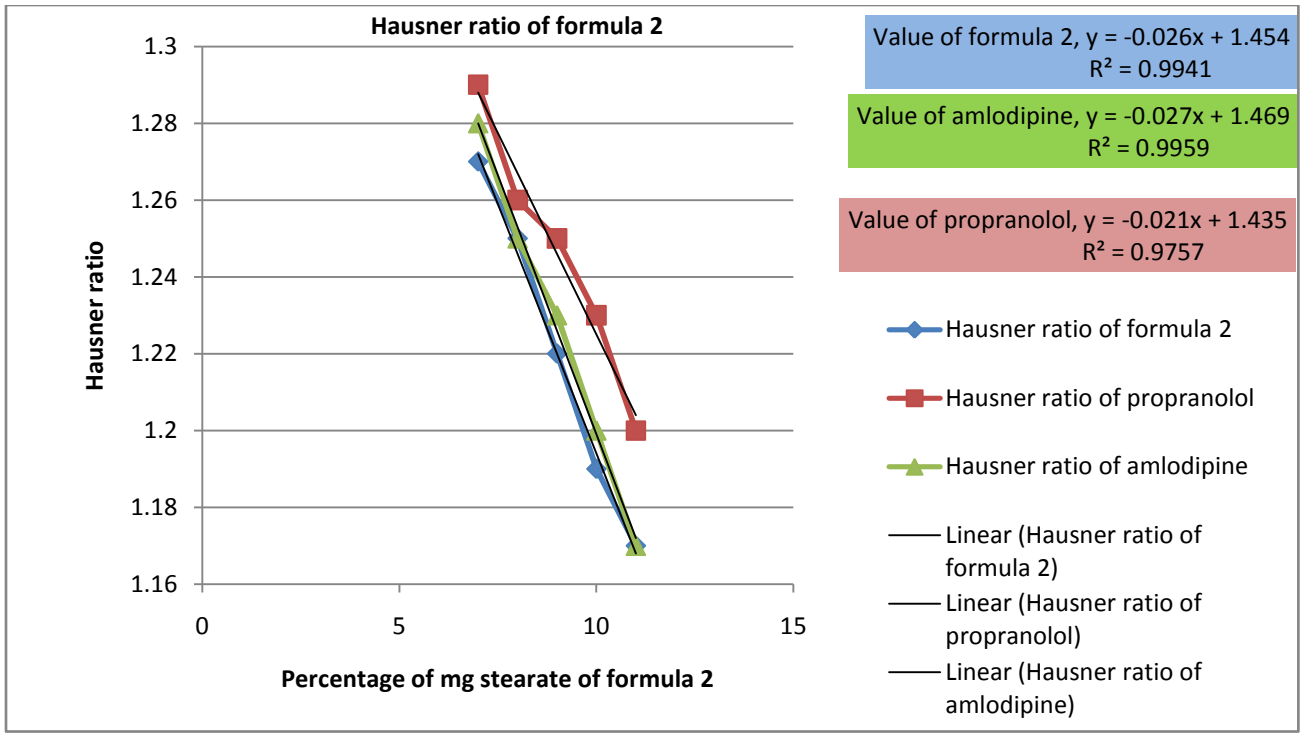

Figure 4.5: A percentage ratio of mg stearate versus Hausner ratio graph

By plotting percentage ratio of mg stearate in X-axis and respected angle of repose in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, angle of repose of formulas, amlodipine and propranolol can be achieved and comparison can made.

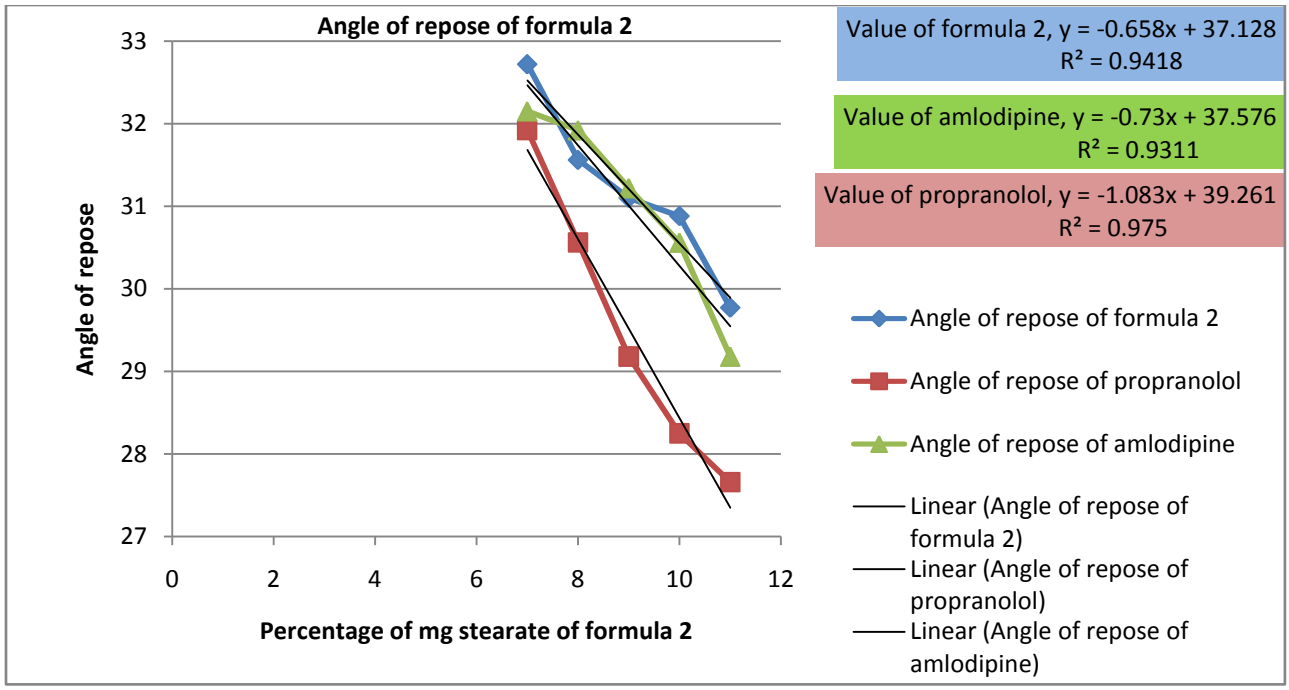

Figure 4.6: A percentage ratio of mg stearate versus angle of repose graph

4.4.3 Comparison between the values of formulas, amlodipine and propranolol for set 3:

By plotting percentage ratio of mg stearate in X-axis and respected Carr's index in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, Carr's index of formulas, amlodipine and propranolol can be achieved and comparison can made.

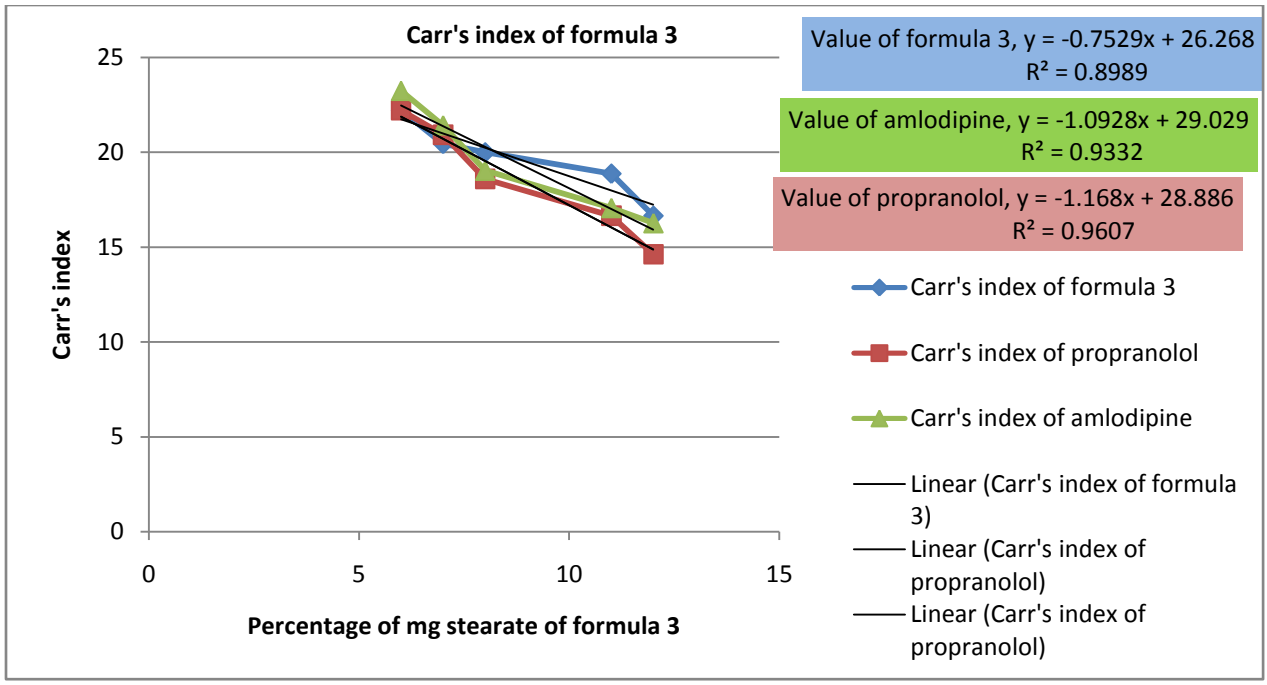

Figure 4.7: A percentage ratio of mg stearate versus Carr's index graph

By plotting percentage ratio of mg stearate in X-axis and respected Hausner ratio in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, Hausner ratio of formulas, amlodipine and propranolol can be achieved and comparison can made.

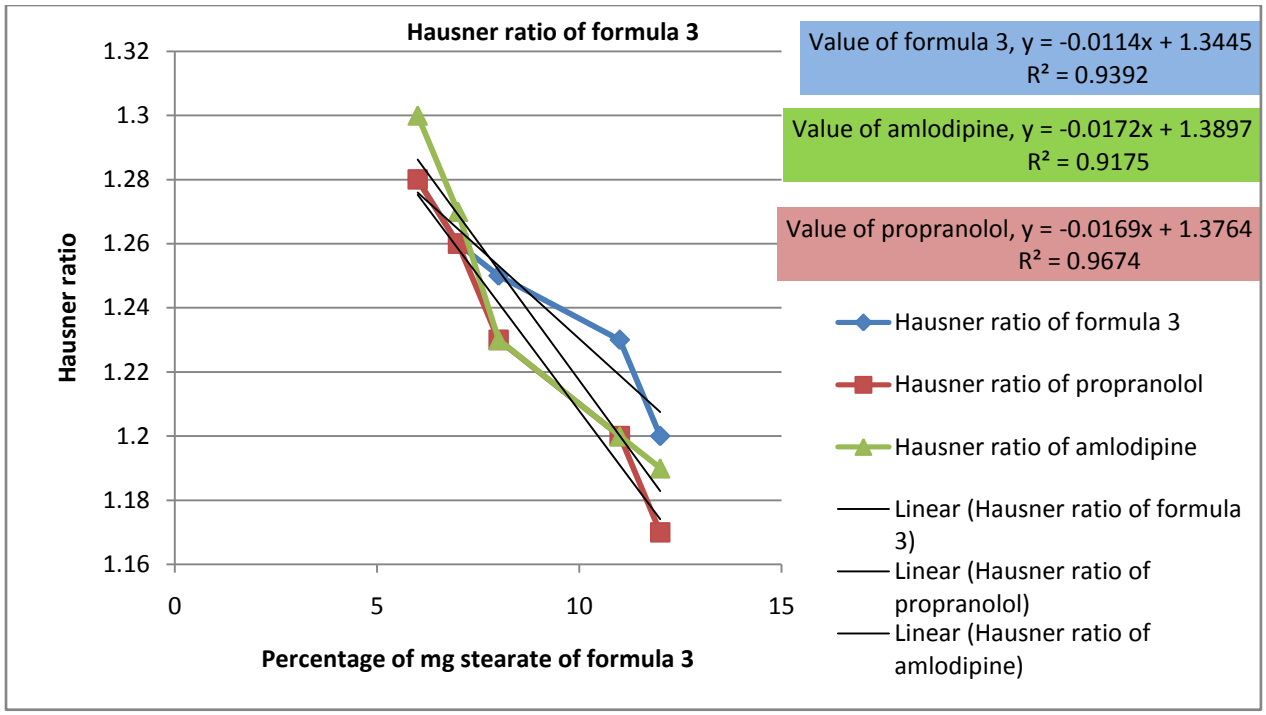

Figure 4.8: A percentage ratio of mg stearate versus Hausner ratio graph

By plotting percentage ratio of mg stearate in X-axis and respected angle of repose in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, angle of repose of formulas, amlodipine and propranolol can be achieved and comparison can made.

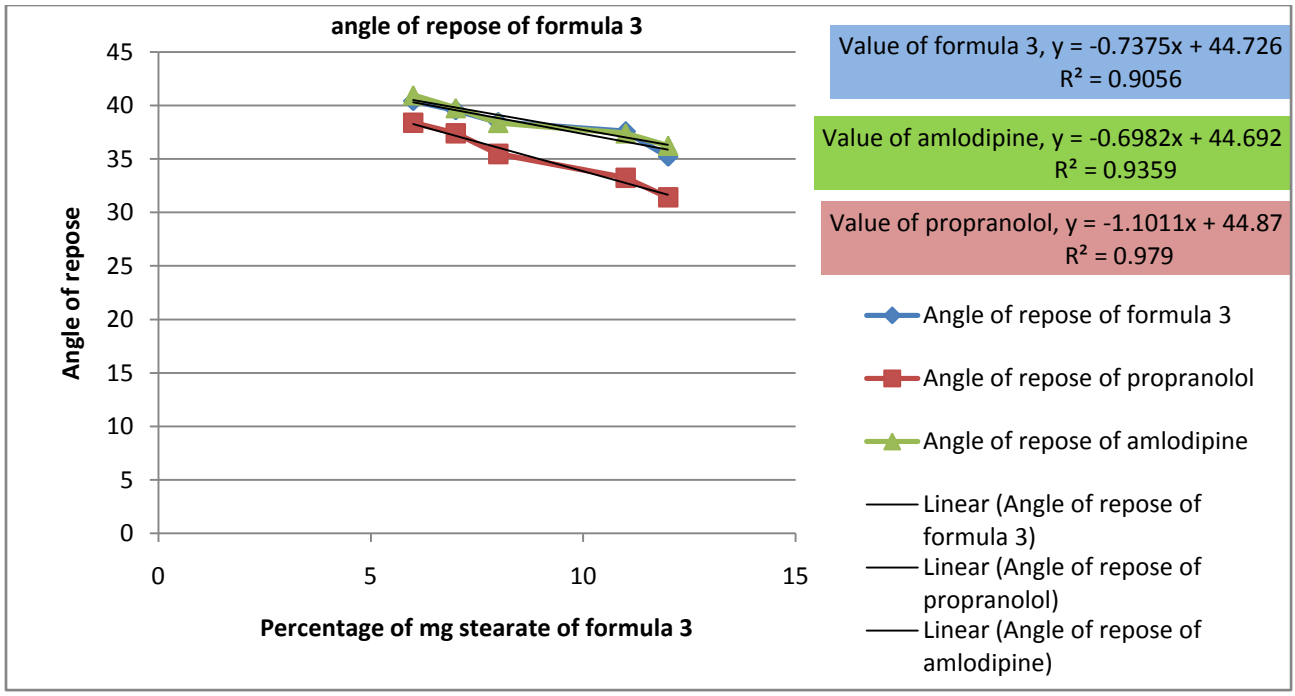

Figure 4.9: A percentage ratio of mg stearate versus angle of repose graph

4.4.4 Comparison between the values of formulas, amlodipine and propranolol for set 4:

By plotting percentage ratio of mg stearate in X-axis and respected Carr's index in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, Carr's index of formulas, amlodipine and propanolol can be achieved and comparison can made.

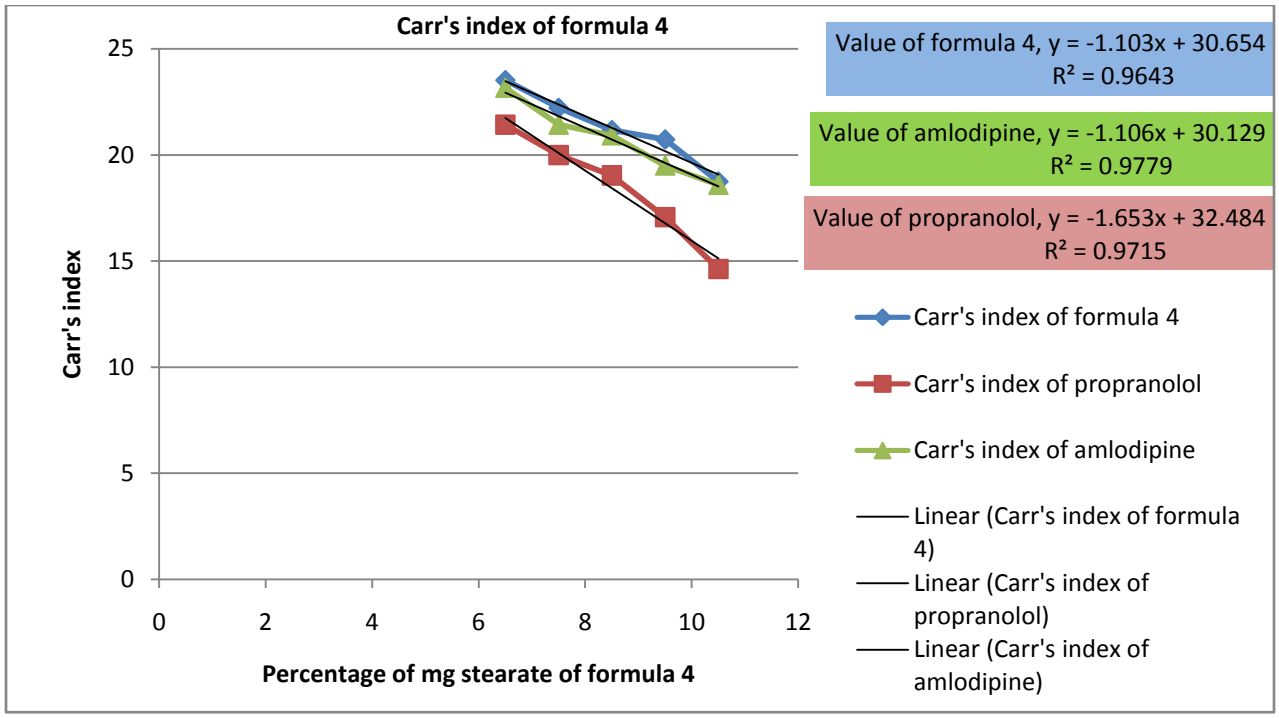

Figure 4.10: A percentage ratio of mg stearate versus Carr's index graph

By plotting percentage ratio of mg stearate in X-axis and respected Hausner ratio in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, Hausner ratio of formulas, amlodipine and propranolol can be achieved and comparison can made.

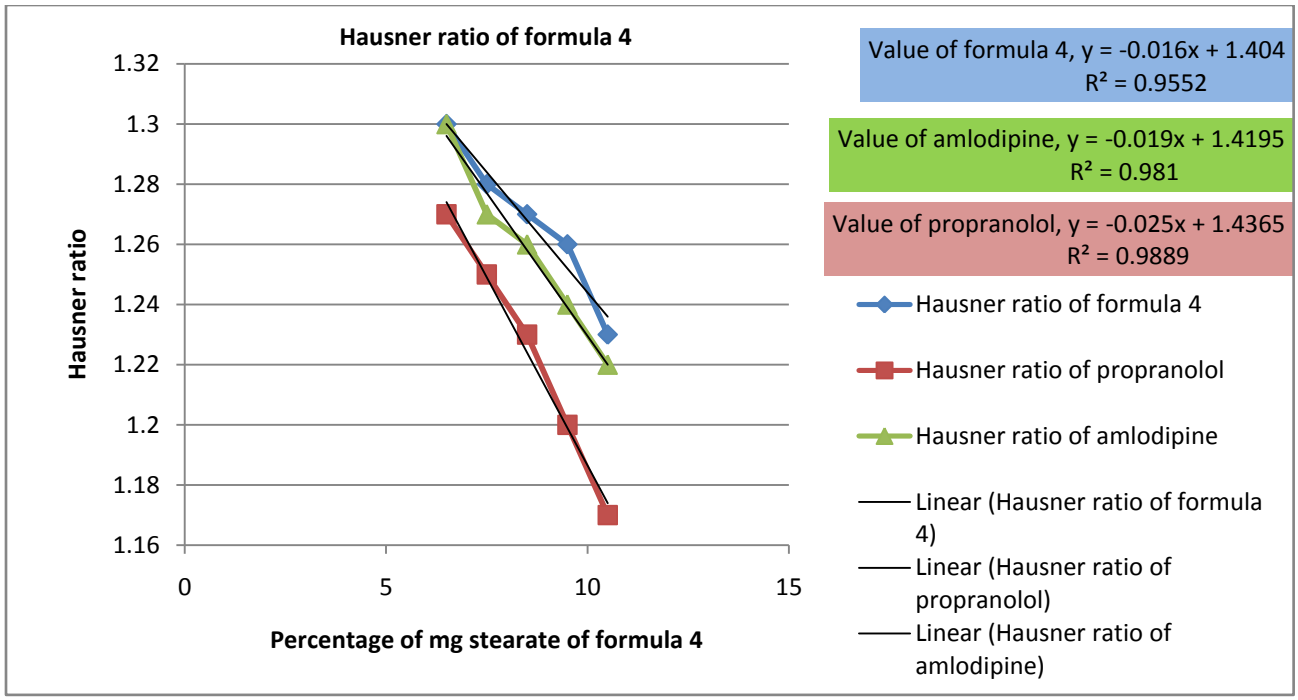

Figure 4.11: A percentage ratio of mg stearate versus Hausner ratio graph

By plotting percentage ratio of mg stearate in X-axis and respected angle of repose in Y-axis, a graph is plotted by which an equation and regression value was established. Using these equations, angle of repose of formulas, amlodipine and propranolol can be achieved and comparison can made.

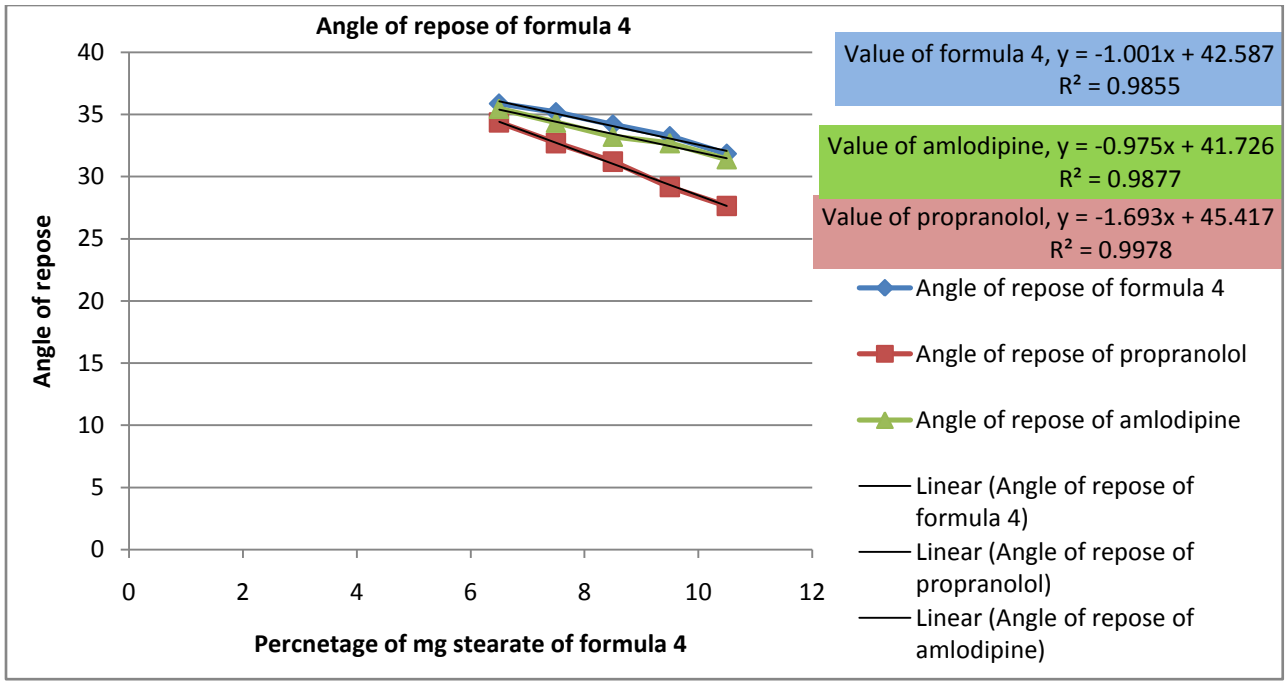

Figure 4.12: A percentage ratio of mg stearate versus angle of repose graph

4.5 Equation and regression value of graph:

4.5.1 Equation and regression value for Carr's index:

Table 4.25: Equation and regression value for Carr's index

Carr's index	**Equation and regression value**
Set 1	Y= -0.4334x+32.09 , R^2= 0.9991…. (i)
Set 2	Y= -1.845x+34.949 , R^2= 0.9893….(ii)
Set 3	Y= -0.7529x+26.268 , R^2= 0.8989….(iii)
Set 4	Y= -1.103x+30.653 , R^2= 0.9643….(iv)
Value of amlodipine for set 1	Y= -0.404x+31.188 , R^2= 0.991….(v)
Value of amlodipine for set 2	Y= -1.852x+35.09 , R^2= 0.9962….(vi)
Value of amlodipine for set 3	Y= -1.0928x+29.029 , R^2= 0.9332….(vii)
Value of amlodipine for set 4	Y= -1.103x+30.129 , R^2= 0.9779….(viii)
Value of propranolol for set 1	Y= -0.4488x+30.574 , R^2= 0.9326….(ix)
Value of propranolol for set 2	Y= -1.459x+32.699 , R^2= 0.973….(x)
Value of propranolol for set 3	Y= -1.168x+28.886 , R^2= 0.9607….(xi)
Value of propranolol for set 4	Y= -1.653x+32.485 , R^2= 0.9715….(xii)

4.5.2 Equation and regression value for Hausner ratio:

Table 4.26: Equation and regression value for Huasner ratio

Haunser ratio	**Equation and regression value**
Set 1	Y= -0.0075x+1.4574 , R^2= 0.9913….(i)
Set 2	Y= -0.026x+1.454 , R^2= 0.9941….(ii)
Set 3	Y= -0.0114x+1.3445 , R^2= 0.9392….(iii)
Set 4	Y= -0.016x+1.404 , R^2= 0.9552….(iv)
Value of amlodipine for set 1	Y= -0.067x+1.4323 , R^2= 0.9689….(v)
Value of amlodipine for set 2	Y= -0.027x+1.469 , R^2= 0.9959….(vi)

Value of amlodipine for set 3	Y= -0.0172x+1.3897 , R^2= 0.9674….(vii)
Value of amlodipine for set 4	Y= -0.019x+1.4195 , R^2= 0.981….(viii)
Value of propranolol for set 1	Y= -0.0073x+1.4203 , R^2= 0.943….(ix)
Value of propranolol for set 2	Y= -0.021x+1.435 , R^2= 0.9757….(x)
Value of propranolol for set 3	Y= -0.0169x+1.3764 , R^2= 0.9674….(xi)
Value of propranolol for set 4	Y= -0.025x+1.4365 , R^2= 0.9889….(xii)

4.5.3 Equation and regression value for angle of repose:

Table 4.27: Equation and regression value for angle of repose

Angle of repose	**Equation and regression value**
Set 1	Y= -0.328x+48.156 , R^2= 0.9259….(i)
Set 2	Y= -0.658x+37.128 , R^2= 0.9418….(ii)
Set 3	Y= -0.7372x+44.726 , R^2= 0.9056….(iii)
Set 4	Y= -1.001x+42.587 , R^2= 0.9855….(iv)
Value of amlodipine for set 1	Y= -0.3426x+46.415 , R^2= 0.9427….(v)
Value of amlodipine for set 2	Y= -0.73x+37.576 , R^2= 0.9311….(vi)
Value of amlodipine for set 3	Y= -0.6982x+44.692 , R^2= 0.9359….(vii)
Value of amlodipine for set 4	Y= -0.975x+41.726 , R^2= 0.9877….(viii)
Value of propranolol for set 1	Y= -0.3376x+45.348 , R^2= 0.9303….(ix)
Value of propranolol for set 2	Y= -1.083x+39.261 , R^2= 0.975….(x)
Value of propranolol for set 3	Y= -1.0111x+44.87 , R^2= 0.979….(xi)
Value of propranolol for set 4	Y= -1.693x+45.416 , R^2= 0.9978….(xii)

Chapter 5

Discussion

5.1 DISCUSSION

This work was proposed to determine flow properties of different set of pharmaceutical excipients with different types of active pharmaceutical ingredients (API). 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. Anti adherent was 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 and the API. The values of Carr's index, Hausner ratio and angle of repose were plotted against the percentage ratios of anti adherent. 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 API.

The research work has demonstrated that flow property of different ratio of anti adherent and formulas did not maintain the same rule. Sometimes the set of ratio having larger quantity of anti adherent 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 and API against variable ratio of Mg stearate was discussed below with some observed deviations.

- In the case of set-1, the calculated value (Table 4.1, 4.2) and graph (Figure 4.1, 4.2, 4.3) signified that, the values of the Carr's index, Hausner ratio and angle of repose gradually decreased with the increasing ratio of mg stearate 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 mg stearate and formula-1 is 22%:78%. From table 4.1, it can also be said that the values of Carr's index and Hausner ratio lied in between the passable range (Table 1.2).

The measured value of angle of repose (Table 4.2) for 22%:78% (mg stearate: F1) also lied in between the passable range according to Table 1.1.

After that amlodipine and propranolol was mixed with the formula 1 and the flow property was measured using carr's index, hausner ratio and angle of repose (Table 4.9, 4.10, 4.17, 4.18). The values of carr's index, hausner ratio and angle of repose was in between passable to fair range. After that the comparison between the three graph was done.
(Figure 4.1, 4.2, 4.3). From the table 4.25 the equation (i) where y= -0.4334x+32.09. if the value of carr's index (y) is 10 then the percentage of mg stearate 50.96 is needed.

- In the case of set-2, the calculated value (Table 4.3, 4.4) and graph (Figure 4.4, 4.5, 4.6) signified that, the values of the Carr's index, Hausner ratio and angle of repose gradually decreased with the increasing ratio of mg stearate 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 mg stearate and formula-1 is 11%:89%. From table 4.3, it can also be said that the values of Carr's index and Hausner ratio lied in between fair to good range (Table 1.2). The measured value of angle of repose (Table 4.4) for 11%:89% (mg stearate: F1) also lied in between the fair to good range according to Table 1.1.

  After that amlodipine and propranolol was mixed with the formula 2 and the flow property was measured using carr's index, hausner ratio and angle of repose (Table 4.11, 4.12, 4.19, 4.20). There was a slight change due to adding active ingredients and the change in values was not consistant. The values of carr's index, hausner ratio and angle of repose was also in between fair to good range. After that the comparison between the three graph was done (Figure 4.4, 4.5, 4.6). From the table 4.26 the equation (i) where y= -0.328x+48.156. If the value of angle of repose (y) is 25 then the percentage of mg stearate 70.59 is needed.

- In the case of set-3, the calculated value (Table 4.5, 4.6) signified that, the values of the Carr's index, Hausner ratio and angle of repose gradually decreased with the increasing ratio of mg stearate 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 mg stearate and formula-1 is 11%:89%. From table 4.5, it can also be said that the values of Carr's index and Hausner ratio lied in between passable to fair range (Table 1.2). The measured value of angle of repose (Table 4.6) for 11%:89% (mg stearate: F1) also lied in between the fair to good range according to Table 1.1.

  After that amlodipine and propranolol was mixed with the formula 3 and the flow property was measured using carr's index, hausner ratio and angle of repose (Table 4.13, 4.14, 4.21, 4.22). There was a slight change due to adding active ingredients and the change in values was not consistant. The values of carr's index, hausner ratio and angle of repose was also in between fair to good range. After that the comparison between the three graph was done (Figure 4.7, 4.8, 4.9). From the table 4.27 the equation (i) where y= -0.0075x+1.4574. If the value of angle of repose (y) is 1.1 then the percentage of mg stearate 47.65 is needed.

- In the case of set-4, the calculated value (Table 4.7, 4.8) signified that, the values of the Carr's index, Hausner ratio and angle of repose gradually decreased with the increasing ratio of mg stearate 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 mg stearate and formula-1 is 10.5%:89.5%. From table 4.7, it can also be said that the values of Carr's index and Hausner ratio lied in between passable to fair range (Table 1.2). The measured value of angle of repose (Table 4.8) for 10.5%:89.5% (mg stearate: F1) also lied in between the good range according to Table 1.1.

After that amlodipine and propranolol was mixed with the formula 4 and the flow property was measured using carr's index, hausner ratio and angle of repose (Table 4.15, 4.16, 4.23, 4.24). The values of Carr's index, Hausner ratio was in between fair to good and angle of repose was also in between good to excellent range. After that the comparison between the three graph was done (Figure 4.10, 4.11, 4.12).

Chapter 6

Conclusion

6.1 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 flow ability 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 and also by mixing the active ingredients to determine any change in the flow property. Variation of flow property of different set of formulas of excipients against variable ratio of anti adherent was observed and the most suitable ratio of anti adherent and a defined set of other excipients (formulas) were proposed that showed better flow ability. 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 anti adherent. This would help any future query about the flow property of any set of excipients with the active ingredients in different ratios.

Chapter 7

References

7.1 REFERENCES

Amidon, G.E., Houghton, M.E. (1995). The effect of moisture on the mechanical and powder flow properties of microcrystalline cellulose. *Pharmaceutical Research* [online] 12 (6), 923-929. Available at: http://link.springer.com/article/10.1023/A:1016233725612 [Accessed on 14 November, 2015].

Bhattachar, S.N., Hedden, D.B., Olsofsky, A.M., Qu, X., Hsieh, WY., Canter, K.G. (2004). Evaluation of the vibratory feeder method for assessment of powder flow properties. *International Journal of Pharmaceutics* [Online] 269 (2), 385-392. Available at: http://www.sciencedirect.com/science/article/pii/S0378517303005271 [Accessed on 18 November, 2015]

Bolhuis, G. K., Lerk, C.F., Moes, J.R. (1979). Comparative evaluation of excipients for direct compression. *Pharmaceutisch Weekblad* [Online] 1 (1), 1473-1482. Available at: http://link.springer.com/article/10.1007/BF02293487 [Accessed on 18 Novenmebr, 2015]

Chowhan, Z.T., Yang, I.C. (1983) Powder flow studies IV. Tensile strength and orifice flow rate relationships of binary mixtures. *International Journal of Pharmaceutics* [Online] 14 (2-3), 231-242.
Available at: http://www.sciencedirect.com/science/article/pii/0378517383900960 [Accessed on 18 November, 2015]

Copleyscientific (2012). Powders flow ability testers: angle of repose. Available at: http://www.copleyscientific.com/editorials.asp?c=210&d=3 [Accessed on 10 Novenmebr, 2015]

Crouter, A. and Timothy, L., 2013. The Effect of Moisture on the Flowability of Pharmaceutical Excipients, *Pharma Gate Way*, [online] Available at: http://www.pharmagateway.net/ArticlePage.aspx?doi=10.1208/s12249-013-0036- 0. [Accessed on 16 November, 2015].

Dow (2011). Lubricants. Available at: http://www.dow.com/polyglycols/polyethylene/applications/lubricants.htm [Accessed on 10 Novenmebr, 2015]

Drug bank (2005). Mechanism of action of propanolol. Available at: http://www.drugbank.ca/drugs/DB00571 [Accessed on 10 november, 2015]

Drugs.com (2013). Diluents. Available at: http://www.drugs.com/dict/diluents.html [Accessed on 8 November, 2015]

Drugtopics (2008). Overview of pharmaceutical excipients used in tablets and capsules. Available at: http://drugtopics.modernmedicine.com/drug-topics/news/modernmedicine/modern-medicine-news/overview-pharmaceutical-excipients-used-tablets#sthash.dmGGEZY5.dpuf>[Accessed on 8 November, 2015]

Emery, E., Oliver, J.,Pugsley, T., Sharma, J., Zhou, J.(2009).Flowability of moist pharmaceutical powders. *Powder Technology* [Online] 189 (3), 409–415. Available at: http://www.sciencedirect.com/science/article/pii/S0032591008003562 [Accessed 16 November 2015].

Faqih, A.N., Alexander, A.W., Muzzio, F.J., Tomassone, M.S. (2007). A method for predicting hopper flow characteristics of pharmaceutical powders. *Chemical Engineering Science* [Online] 62 (5), 1536–1542. Available at: http://www.sciencedirect.com/science/article/pii/S0009250906007226[Accessed 15 November 2015]

Freemantech (2013). Powder behaviour and the nature of powders. Available at: http://www.freemantech.co.uk/en/powder-flow-and-powder-behavior.html [Accessed on 8 November, 2015]

Flemming, J., Mielck, J.B. (1995). Requirements for the Production of Microtablets: Suitability of Direct-Compression Excipients Estimated from Powder Characteristics and Flow Rates. *Drug Development and Industrial Pharmacy* [Online] 21 (19), 2239-2251. Available at: http://informahealthcare.com/doi/abs/10.3109/03639049509065904 [Accessed on 15 November, 2015]

Gabaude, C.M.D., Gautier, J.C., Saudemon, P., Chulia, D. (2001). Validation of a new pertinent packing coefficient to estimate flow properties of pharmaceutical powders at a very early development stage, by comparison with mercury intrusion and classical flowability methods. *Journal of Materials Science* [Online] 36 (7), 1763-1773. Available at: http://link.springer.com/article/10.1023/A:1017528809955 [Accessed on 18 November, 2015]

Gold, G., Palermo, B.T. (1965). Hopper flow electrostatics of tableting material II. Tablet lubricants. *Journal of Pharmaceutical Sciences* [Online] 54 (10), 1517-1519. Available at: http://onlinelibrary.wiley.com/doi/10.1002/jps.2600541026/abstract [Accessed on 18 November, 2015]

Gold, G., Duvall, R.N., Palermo, B.T., Slater, J.G. (1966). Powder flow studies II. Effect of glidants on flow rate and angle of repose. *Journal of Pharmaceutical Sciences* [Online] 55 (11), 1291-1295. Available at: http://onlinelibrary.wiley.com/doi/10.1002/jps.2600551125/abstract;jsessionid=467D88083A8590F232EE5F1DD15FF455.f02t03?deniedAccessCustomisedMessage=&userIsAuthenticated=false [Accessed on 20 November, 2015]

Hancock, B.C., Carlson, G.T., Ladipo, D.D., Langdon, B.A., Mullarney, M.P. (2001). The powder flow and compact mechanical properties of two recently developed matrix-forming polymers. *Journal of Pharmacy and Pharmacology* [Online] 53 (9), 1193-1199. Available at: http://onlinelibrary.wiley.com/doi/10.1211/0022357011776630/abstract [Accessed on 15 November, 2015]

Hou, H., Sun, C.C. (2008). Quantifying effects of particulate properties on powder flow properties using a ring shear tester. *Journal of Pharmaceutical Sciences* [Online] 97 (9), 4030-4039. Available at: http://onlinelibrary.wiley.com/doi/10.1002/jps.21288/abstract;jsessionid=D78C9F297F341CEFFF03E76ED5A5D62C.f04t01?deniedAccessCustomisedMessage=&userIsAuthenticated=false [Accessed on 15 November, 2015]

Jacob, S., Shirwaikar, A.A., Joseph, A., Srinivasan, K.K. (2007). Novel co-processed excipients of mannitol and microcrystalline cellulose for preparing fast dissolving tablets of glipizide. *Indian Journal of Pharmaceutical Sciences* [Online] 69 (5), 633-639. Available at: http://www.ijpsonline.com/article.asp?issn=0250474X;year=2007;volume=69;issue=5;spage=633;epage=639;aulast=Jacob [Accessed on 15 November, 2015]

Jivraj, M., Martini, L.G., Thomson, C.M. (2000). An overview of the different excipients useful for the direct compression of tablets. *Pharmaceutical Science & Technology Today* [Online] 3 (2), 58-63. Available at: http://www.sciencedirect.com/science/article/pii/S1461534799002370 [Accessed on 15 November, 2013]

Jonat, S., Hasenzahl, S., Drechsler, M., Albers, P., Wagner, K.G., Schmidt, P.C. (2004). Investigation of compacted hydrophilic and hydrophobic colloidal silicon dioxides as glidants for pharmaceutical excipients. *Powder Technology* [Online] 141 (1-2), 31-43. Available at: http://www.sciencedirect.com/science/article/pii/S0032591004000555 [Accessed on 19 November, 2015]

Kachrimanis, K., Petrides, M., Malamataris, S. (2005). Flow rate of some pharmaceutical diluents through die-orifices relevant to mini-tableting. *International Journal of Pharmaceutics* [Online] 303 (1-2), 72-80. Available at: http://www.sciencedirect.com/science/article/pii/S0378517305004588 [Accessed on 15 November, 2015]

Kamath, S., Puri, V.M., Manbeck, H.B. (1994). Flow property measurement using the Jenike cell for wheat flour at various moisture contents and consolidation times. *Powder Technology* [Online] 81 (3), 293–297. Available at: http://www.sciencedirect.com/science/article/pii/0032591094028885 [Accessed on 18 November, 2015]

Kim, E.H., Chen, X.D., Pearce, D. (2005). Effect of surface composition on the flowability of industrial spray-dried dairy powders. *Colloids and Surfaces B: Biointerfaces* [Online] 46 (3), 182-187. Available at: http://www.sciencedirect.com/science/article/pii/S092777650500319X [Accessed on 18 November, 2015]

Lindberg, NO., Pålsson, M., Pihl, AC., Freeman, R., Freeman, T., Zetzener, H., Enstad, G. (2004). Flow Flowability Measurements of Pharmaceutical Powder Mixtures with Poor Flow Using Five Different Techniques. *Drug Development and Industrial Pharmacy* [Online] 30 (7), 785-791. Available at: http://informalhealthcare.com/doi/abs/10.1081/DDC-120040343 [Accessed on 18 November, 2015]

Mckenna, A., Mccafferty, D.F. (1982). Effect of particle size on the compaction mechanism and tensile strength of tablets. *Journal of Pharmacy and Pharmacology* [Online]34 (6). 347-351. Available at: http://onlinelibrary.wiley.com/doi/10.1111/j.2042-7158.1982.tb04727.x/abstract [Accessed on 18 November, 2015]

Mullarney, M.P., Hancock, B.C., Carlson, G.T., Ladipo, D.D., Langdon, B.A. (2003). The powder flow and compact mechanical properties of sucrose and three high-intensity sweeteners used in chewable tablets. *International Journal of Pharmaceutics* [Online] 257 (1-2), 227-236. Available at: http://www.sciencedirect.com/science/article/pii/S0378517303001443 [Accessed on 15 November, 2015]

Nagel, K.M., Peck, G.E. (2003). Investigating the Effects of Excipients on the Powder Flow Characteristics of Theophylline Anhydrous Powder Formulations. *Drug Development and Industrial Pharmacy* [Online] 29 (3), 277-287. Available at: http://informalhealthcare.com/doi/abs/10.1081/DDC-120018201 [Accessed on 18 November, 2015]

Pformulate (2000). What is a disintegrants? Available at: http://www.pformulate.com/disintegrs.htm [Accessed on 8 November, 2015]

Pharmacopeia (2013). Bulk density and Tapped density. Available at: http://www.pharmacopeia.cn/v29240/usp29nf24s0_c616.html [Accessed on 8 November, 2015]

Pharmacopeia (2013). Apendix 1.definitions. Available at: http://www.pharmacopeia.cn/v29240/usp29nf24s0_c1078s63.html [Accessed on 8 November, 2015]

Pharmacopeia (2013). Powder Flow. Available at: http://www.pharmacopeia.cn/v29240/usp29nf24s0_c1174.html [Accessed on 8 November, 2015]

Podczeck, F, Newton, J.M. (2000) Powder and capsule filling properties of lubricated granulated cellulose powder. *Eur J Pharm Biopharm* [Online] 50 (3), 373-7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11072194 [Accessed on 15 November, 2015]

Rowe, R.C., Sheskey, P.J., Owen, S.C. (2005). Monograph. *Handbook of Pharmaceutical Excipients* (5th edition) [Accessed on 18 November, 2015]

Schmidt, P.C., Rubensdörfer, C.J.W. (1994). Evaluation of Ludipress as a "Multipurpose Excipeent" for Direct Compression: Part I: Powder Characteristics and Tableting Properties. *Drug Development and Industrial Pharmacy* [Online] 20 (18), 2899-2925. Available at: http://informahealthcare.com/doi/abs/10.3109/03639049409042687 [Accessed on 19 November, 2015]

Seppala, K., Heinamaki, J., Hatara, J., Seppala, L., Yliruusi, J. (2010). Development of a New Method to Get a Reliable Powder Flow Characteristics Using Only 1 to 2 g of Powder. AAPS PharmSciTech [Online] 11 (1), 402-408.

Available at: http://link.springer.com/article/10.1208/s12249-010-9397-9 [Accessed on 16 November, 2015]

Shah, R.B., Tawakkul, M.A., Khan, M.A. (2008) Comparative Evaluation of Flow for Pharmaceutical Powders and Granules. *AAPS PharmSciTech* [Online] 9 (1), 250-258. Available at: http://link.springer.com/article/10.1208/s12249-008-9046-8 [Accessed on 15 November, 2013].

Silva, J. P. S., Splendor, D., Gonçalves, I. M. B., Costa P. and Lobo J. M. S., 2013. Note on the Measurement of Bulk Density and Tapped Density of Powders According to the European Pharmacopeia. *Pharma Gate Way*, [online] Available at: http://www.pharmagateway.net/ArticlePage.aspx?doi=10.1208/s12249-013-9994-5. [Accessed on 16 November, 2015].

Sinka, I.C., Schneider, L.C.R., Cocks, A.C.F. (2004). Measurement of the flow properties of powders with special reference to die fill. *International Journal of Pharmaceutics* [Online] 280 (1-2), 27-38. Available at: http://www.sciencedirect.com/science/article/pii/S0378517304002832 [Accessed on 19 November, 2015]

Slideshare (2012). Particle and powder density, Hausner index and Carr's ratio. Available at: http://www.slideshare.net/haroon41us/Hausner-ratio [Accessed on 8 November, 2015]

Sun, C.C. (2010). Setting the bar for powder flow properties in successful high speed tableting. *Powder Technology* [Online] 201 (1), 106-108. Available at: http://www.sciencedirect.com/science/article/pii/S0032591010001300 [Accessed on 16 November, 2015]

Talukdar, M.M., Michoel, A., Rombaut, P., Kinget, R. (1996). Comparative study on xanthan gum and hydroxypropylmethyl cellulose as matrices for controlled-release drug delivery I. Compaction and in vitro drug release behaviour. *International Journal of Pharmaceutics* [Online] 129 (1-2), 233-241. Available at: http://www.sciencedirect.com/science/article/pii/0378517395043551 [Accessed on 15 November, 2015]

Tan, S.B., Newton, J.M. (1990). Powder flowability as an indication of capsule filling performance. *International Journal of Pharmaceutics* [Online] 61 (1-2), 145-155. Available at: http://www.sciencedirect.com/science/article/pii/0378517390900537 [Accessed on 18 November, 2015].

Taylor, M.K., Ginsburg, J., Hickey, A.J. Gheyas, F. (2000). Composite method to quantify powder flow as a screening method in early tablet or capsule formulation development. *AAPS PharmSciTech* [Online] 1 (3), 20-30. Available at: http://link.springer.com/article/10.1208/pt010318 [Accessed on 18 November, 2015]

Thalberg, K., Lindholm, D., Axelsson, A. (2004) Comparison of different flowability tests for powders for inhalation. *Powder Technology* [Online] 146 (3), 206-213. Available at: http://www.sciencedirect.com/science/article/pii/S0032591004003225 [Accessed on 19 November, 2015]

Trainaa, K. Clootsb, R., Bontempia, S., Lumayc, G., Vandewallec, N. and Boschini F., 2013. Flow abilities of powders and granular materials evidenced from dynamical tap density measurement, *Science Direct*, [online] Available at: http://www.sciencedirect.com/science/article/pii/S0032591012007887. [Accessed on 16 November, 2015].

Vanarase, A.U., Osorio, J.G., Muzzio, F.J. (2013). Effects of powder flow properties and shear environment on the performance of continuous mixing of pharmaceutical powders. *Powder Technology* [Online] 246, 63–72. Available at: http://www.sciencedirect.com/science/article/pii/S0032591013003471 [Accessed on 16 November, 2015]

Vinensia (2013). Diluents for tablet formulation. Available at: http://formulation.vinensia.com/2011/11/diluents-fillers-for-tablet-formulation.html [Accessed on 8 November, 2015]

Yu, W., Muteki, K., Zhang, L., Kim, G. (2010) Prediction of bulk powder flow performance using comprehensive particle size and particle shape distributions. *Journal of Pharmaceutical Sciences* [Online] 100 (1), 284-293. Available at: http://onlinelibrary.wiley.com/doi/10.1002/jps.22254/full [Accessed on 16 November, 2015]

Zhang, Y.,Law, Y., Chakrabarti, S. (2003) Physical properties and compact analysis of commonly used direct compression binders. *AAPS PharmSciTech* [Online] 4 (4), 489-499. Available at: http://link.springer.com/article/10.1208/pt040462 [Accessed on 18 November, 2015].