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

Submitted By

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

DECLARATION BY THE CANDIDATE

I, **Tasnim Iffat**, hereby declare that this dissertation, entitled "**DETERMINATION OF VARIATION IN FLOW PROPERTY OF DIFFERENT FORMULAS OF STARCH ALONG WITH AMLODIPINE AND PROPRANOLOL**" submitted by me to the Department of Pharmacy, East West University is an authentic and genuine thesis project carried out by me under the supervision and guidance of **Mr. Md. Anisur Rahman**, Senior Lecturer, Department of Pharmacy, East West University, Dhaka.

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CERTIFICATE BY THE SUPERVISOR

This is to certify that the dissertation entitled **"DETERMINATION OF VARIATION IN FLOW PROPERTY OF DIFFERENT FORMULAS OF STARCH ALONG WITH AMLODIPINE AND PROPRANOLOL"**, submitted to the Department of Pharmacy, East West University, in partial fulfillment of the requirements for the Degree of Bachelor of Pharmacy, by **Tasnim Iffat** under my supervision. I further certify that it is a genuine research work and no part of the thesis has been submitted elsewhere for any other degree/diploma and all the resources of the information in thus connection are duly acknowledged.

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ENDORSEMENT BY THE CHAIRPERSON

This is to certify that the dissertation entitled "**DETERMINATION OF VARIATION IN FLOW PROPERTY OF DIFFERENT FORMULAS OF STARCH ALONG WITH AMLODIPINE AND PROPRANOLOL**" submitted by Tasnim Iffat is a genuine research work under the supervision of **Mr. Md. Anisur Rahman** (Senior Lecturer, Department of Pharmacy, East West University, Dhaka). I further certify that no part of the thesis has been submitted for any other degree and all the resources of the information in thus connection are duly acknowledged.

Shamsun Nahar Khan Ph.D.

Associate Professor & Chairperson,

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East West University.

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Dedication

This Research Paper is Dedicated

To

My Beloved Parents

ABSTRACT

This work was proposed to determine the flow properties of different set of pharmaceutical excipients formulations that are directly compressible tablets and to search for some equations which can predict the flow property of the excipients with different ratio of diluents. Here we determine the flow property of formulation with amlodipine and propranolol and compare with excipient formulation. Compressibility index, Hausner ratio, and angle of repose were used as as a parameters of determining flow properties. Diluents were mixed with these prepared formulas in different specific and justified ratio. The prepared mixture in a constant weight was then examined for measuring flow property with and without APIs. The values of Carr's index, Hausner ratio and angle of repose were plotted against the percentage ratios of diluents. The study showed a linear relationship with different ratios of mixture and flow property measuring parameters. From these graphs the straight line equation for each set of formula were obtained regression value which can be used to predict the flow property of these formula with different ratio of diluents. Moreover the most suitable ratio of specific diluents and a specific set of other excipients were proposed that showed better flow property with amlodipine and propranolol. These equations can be used for other APIs also to determine their flow property.

Keywords: Excipient, Hausner's ratio, Carr's index, Angle of repose, Flow property, Diluent, Amlodipine, Propranolol.

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Introduction

1.1 Introduction

In the pharmaceutical industry uniform flow of powders is one of the most important considerations in solid dosage manufacture. Investigation into the properties affecting powder flow is crucial. The powders flow behavior is a key factor in a series of unit processes such as blending, compression, filling, transportation and in scale-up operations. In tablets compression and capsules filling, an optimal powder flow must be achieved in order to produce final products with an acceptable uniformity content, weight variation and physical consistence.

The objective of this experiment was to identify the nature of flow of a particular formulation prepared only by various powdered excipients with different amount of diluent (starch). Another objective of this research was to evaluate that ratio of pharmaceutical excipients in a mixture with API (amlodipine and propranolol) that will provide maximum flow property. We were focusing to identify a specific equation which will explain the flow ability of this formulation with different API (amlodipine and propranolol). Our proposed equations will be helpful for determining the flow property of new drug formulations. We had measured several parameters, such as, bulk density, tapped density, Carr's index, Hausner ratio and angle of repose for different mixture of same pharmaceutical excipients but in different ratio, and were able to resolve an equation. We had done this for different mixtures of different excipients to determine different equations. Our proposed equation will help the future researcher to evaluate the flowability variation occurred due to the variable percentages of different excipients.

1.2 Powder flow

A simple definition of powder flowability is the ability of a powder to flow. By this definition, flowability is sometimes thought of as a one-dimensional characteristic of a powder, whereby powders can be ranked on a sliding scale from "free-flowing" to "non-flowing". The inability to

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

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

(Freemantech, 2013)

1.3 Importance of flow property in powder material

- It is really important for a pharmaceutical manufacturer to check about the flow property of the formulation for any solid dosage form preparation. The same powder may flow well in one hopper but poorly in another; likewise, a given hopper may handle one powder well but cause another powder to hang-up.

- It is required to have knowledge of the flowability of any single powder or a bulk because it helps in designing powder handling equipment such as hoppers that no flow problems (flow impediments, segregation, or any irregular flow, etc.) will occur.

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

- A team from product development can assess new excipients, active drugs and formulations, predicting their behavior prior to inauguration of large-scale production. They can also check how new powders (excipients) interact with existing ingredients. This speeds up development time and which minimizes errors during final production. And this strategy is really beneficial when active ingredients or any inactive materials are extremely valuable and may have only been produced in undersized quantities.

- 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. (Young, 20113)

1.4 Factors affecting the powder flow property

Powders are probably the least predictable of all materials in relation to flow ability because of the large number of factors that can change their rheological properties. For example: fine particles tend to be more cohesive and therefore less free flowing whereas larger denser particles tend to be more flowing. Another example is 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. Flow Properties of powders depend upon:

- Collective forces acting on individual particles
- particle variables environmental conditions
- particle size distribution
- Shape
- Cohesiveness

- surface texture
- surface coating
- particle interaction
- electrostatic charge

Other factors include hardness, stiffness, strength, compaction condition, humidity etc.

However, there are numerous variations of these methods, test methodology and operating scheme for measuring the flow property of powders. They are:

- angle of repose
- compressibility index or Hausner ratio
- Flow rate through an orifice, and
- Shear cell.

In this research we use angle of repose, compressibility index and hausner ratio to determine the flow property of powder.

(Slideshare, 2013)

1.5 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. Hence, the bulk density depends on both the density of powder particles and the spatial arrangement of particles in the powder bed. The bulk density is expressed in grams per millilitre (g/ml) although the international unit is kilogram per cubic metre (1 g/ml = 1000 kg/m3) because the measurements are made using cylinders.It may also be expressed in grams per cubic centimetre (g/cm3).

The bulking properties of a powder are dependent upon the preparation, treatment and storage of the sample. The particles can be packed to have a range of bulk densities and, moreover, the

slightest disturbance of the powder bed may result in a changed bulk density. Thus, the bulk density of a powder is often very difficult to measure with good reproducibility and, in reporting the results, it is essential to specify how the determination was made.

(British Pharmacopeia, 2013)

1.6 Tapped density

The tapped density is obtained by mechanically tapping a graduated measuring cylinder or vessel containing the powder sample. After observing the initial powder volume or mass, the measuring cylinder or vessel is mechanically tapped, and volume or mass readings are taken until little further volume or mass change is observed.The tapping is achieved by raising the cylinder and allowing it to drop under a specified distance

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

(WHO, 2012)

1.7 Factors influencing bulk density and tapped density

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

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

(British Pharmacopeia, 2013)

1.8 MEASURES OF POWDER COMPRESSIBILITY

The Compressibility index and Hausner ratio are measures of the propensity of a powder to be compressed as described above. As such, they are measures of the powder ability to settle and they permit an assessment of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticulate interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index and the Hausner Ratio.

1.8.1 Carr's 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.

Compressibility index:

$$100 \times \frac{(bulk\ volume - true\ volume)}{bulk\ volume}$$

(Slideshare, 2012)

1.8.2 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.

Hausner Ratio:

$$\frac{bulk\ volume}{true\ volume}$$

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

Compressibility index:

$$100 \times \frac{(true\ density - bulk\ density)}{true\ density}$$

Hausner ratio:

$$\frac{true\ density}{bulk\ density}$$

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

(Slideshare, 2012)

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

Car's index	Flow character	Hausner ratio
≤ 10	Excellent	1.0-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-30	Poor	1.35-1.45
31-35	Very Poor	1.46-1.59
>38	Very, Very poor	>1.60

1.8.3. Relation between Carr's index and Hausner ratio

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

$$H=100/ (100-C)$$

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

1.9 Angle of repose

The angle of repose is the constant, three-dimensional angle (relative to the horizontal base) assumed by a cone-like pile of material formed by any of several different methods. The angle of repose is used in the several branches of science to characterize the flow properties of solids. Angle of repose is interring particulate friction or resistance to movement between particles. Angle of repose test results is reported to be very dependent upon the method used. Experimental difficulties arise as a result of segregation of material and consolidation or aeration of the powder as the cone is formed. The method continues to be used in the pharmaceutical industry.

The angle of repose can range from 0° to 90°. Lower the angle of repose, better the flow property

Figure 1.1: measuring of height of cone (Merriam, 2013)

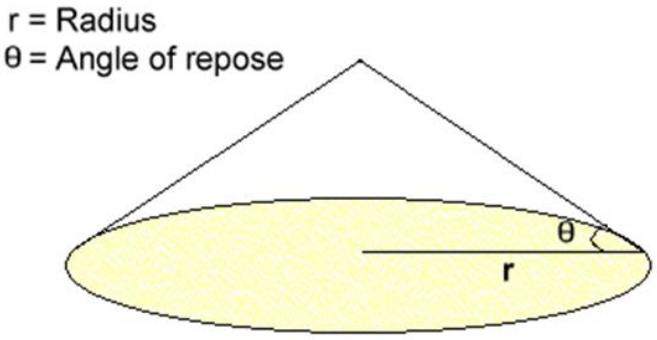

Figure.1.2: Angle of repose (Merriam, 2013)

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 can be calculated by the following formula.

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

(Merriam, 2013)

1.2 Table: Relation between flow properties and angle of repose

Flow property	Angle of repose
Excellent	**25-30**
Good	**31-35**

Fair	**36-40**
Passable	**41-45**
Poor	**46-55**
Very poor	**56-65**
Very, very poor	**>66**

1.9.1 Factors affecting the angle of repose

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

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

(Authorstream, 2013)

1.10: Pharmaceutical Excipients

An excipient is a natural or synthetic substance formulated alongside the active ingredient of a medication, included for the purpose of long-term stabilization, bulking up solid formulations that contain potent active ingredients or to confer a therapeutic enhancement on the active

ingredient in the final dosage form, such as facilitating drug absorption, reducing viscosity or enhancing solubility. Excipients can also be useful in the manufacturing process, to aid in the handling of the active substance concerned such as by facilitating powder flowability or non-stick properties, in addition to aiding in vitro stability such as prevention of denaturation or aggregation over the expected shelf life. The selection of appropriate excipients also depends upon the route of administration and the dosage form, as well as the active ingredient and other factors.

(Authorstream, 2013)

1.10.1: Classification of pharmaceutical excipients

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

- Diluents or fillers
- Binders
- Disintegrants
- Glidants
- Lubricants
- Antiadherents

1.10.2: Diluents

Diluents make the required bulk of the tablet when the drug dosage itself is inadequate to produce tablets of adequate weight and size. For example if the active ingredient is just 2 mg, is such a case a tablet of just 2 mg is very difficult to manufacture and handle too, thus the bulk content is increased by addition of inactive excipient. Round tablets of weight 120mg to 700mg and for oval tablets 800mg are easy to handle.

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

(Wikianswers, 2013)

1.10.2.1: Ideal characteristics of diluents

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

(Vinensia, 2013)

1.10.2.2: 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. To combat this problem compatibility test of diluent with the API is done.

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.

(Pformulate, 2000)

1.10.3: Binders

Binders are added to tablet formulations to add cohesiveness to powders, thus providing the necessary bonding to form granules, which under compaction form a cohesive mass or a compact which is referred to as a tablet. Binders hold the ingredients in a tablet together. Binders ensure that tablets and granules can be formed with required mechanical strength, and give volume to low active dose tablets.

Examples: starches, cellulose or modified cellulose such as microcrystalline cellulose and cellulose ethers such as hydroxypropyl cellulose (HPC), polyvinyl pyrrolidone (PVP) and polyethylene glycol etc.

(Vinensia, 2013)

1.10.4: Disintegrants

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

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

1.10.5: Glidants

Glidants are inert excipients that are added to tablet formulations to reduce interparticulate friction and to improve the flow properties of granules from the hopper into the feed mechanism and ultimately into the tablet die.

Talc is an ideal glidant to be used in this dosage form. Concentration of starch is common up to 10%, but should be limited otherwise it will worsen the flow of material. Besides colloidal

silicon dioxide added at a typical level of 0.1% to 0.2% will improve the flow characteristics of a compression mix.

Examples: magnesium stearate, Aerosil (colloidal silicon dioxide), starch, zinc stearate talc etc.

(Drugtopics, 2008)

1.10.7: Lubricants

Lubricants are agents that act by reducing friction by interposing an intermediate layer between the tablet constituents and the die wall during compression and ejection. Solid lubricants, act bt boundary mechanism, results from the adherence of the polar portions of molecules with long carbon chains to the metal surfaces to the die wall. The presence of lubricant coating may cause an increase in the disintegration time and a decrease in drug dissolution rate. The choice of a lubricant may depend upon the type of tablet being manufactured, dissolution, flow characteristics and requirements of the formulation in terms of hardness, friability and compatibility.

Examples: stearates, sterotex, talc, wax, stearowet,boric acid, sodium benzoate, sodium acetate etc.

(Apu, 2010)

1.10.8: Antiadherents

Some materials have strong adhesive properties towards the metal of punches and dies or the tablet formulation containing excessive moisture whith has tendency to result in picking and sticking problem. Therefore antiadherents are added, which prevent stocking to punches and die walls.

Examples: corn starch, colloidal silica,sodium lauryl sulfate, DL- leucine etc.

1.10.9: Miscellaneous

Above from the above mentioned principal ingredients following excipients also improve the dosage form characters. They are used in minute quantities normally to mask the bad smell, color and increase the tablets appearances. They are stabilizers, colorants, flavourants, surfactants etc.

(Drugtopics, 2008)

1.11: SHORT NOTES ON THE EXCIPIENTS USED IN THE EXPERIMENT

1.11.1 Starch

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

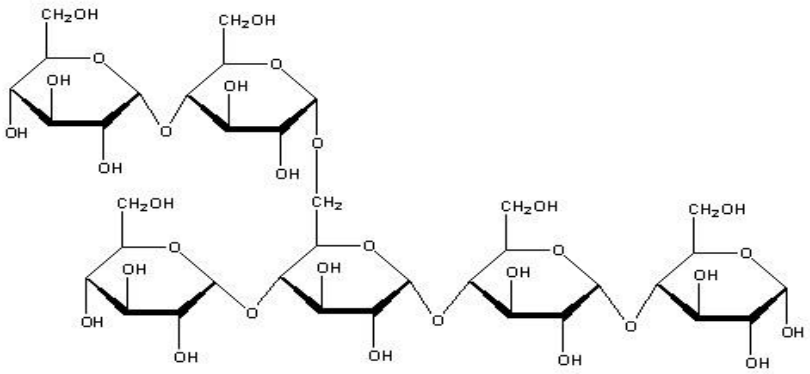

Fig 1.3: starch (Drugtopics, 2008)

1.11.2: Magnesium stearate

Magnesium stearate is often used as an anti-adherent in the manufacture of medical tablets, capsules and powders. In this regard, the substance is also useful, because it has lubricating properties, preventing ingredients from sticking to manufacturing equipment during the compression of chemical powders into solid tablets; magnesium stearate is the most commonly used lubricant for tablets. Magnesium stearate melts at about 88 °C, is not soluble in water, and is generally considered safe for human consumption at levels below 2500 mg/kg per day. It has molecular weight of 591.34.

(Rowe, Sheskey, Owen, 2005)

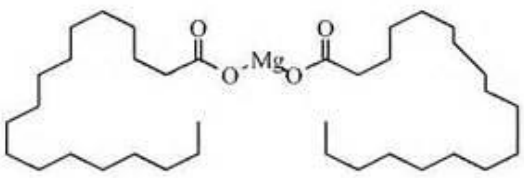

Fig 1.4: magnesium stearate (Rowe, Sheskey, Owen, 2005)

1.11.3 Zinc Stearate

Zinc Stearate is a white coloured poweder. It is insoluble in water, but dissolves well in aromatic compounds like benzene and chlorinated hydrocarbons on heating. It is insoluble in alcohol and ethers. Zinc stearate does not contain any electrolyte.

Zinc stearate is used in the pharmaceutical industry and the cosmetic products like face powder to improve the smoothness and adhesion. It is used in paint industry as a gloss imparting agent and a grinding agent. In plastic and rubber processing, zinc stearate is ued as a releasing agent and lubricant which can be easily incorporated. It is used as as a metal release agent in rubber, polyurethane and polyester processing system.

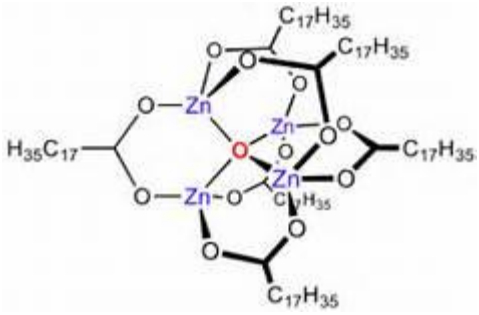

Fig 1.5: zinc stearate (Drugs.com, 2011)

1.11.4: Carboxy methyl cellulose

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 effects the amount of active ingredient absorbed, thereby decreasing effectiveness. Carboxymethylcellulose is available in different salt forms, such as sodium or calcium.

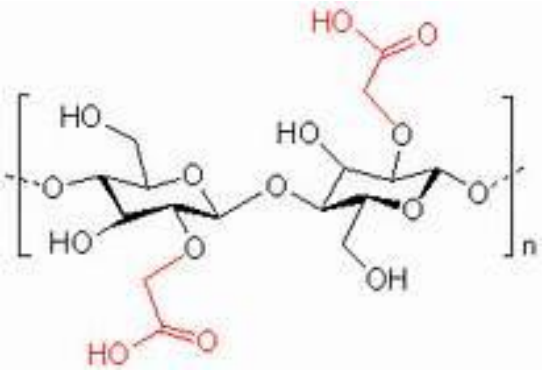

Fig 1.6: Carboxy methyl cellulose (Dow, 2011)

1.11.5: Polyethylene glycol (PEG)

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

(Dow, 2011)

1.11.6 Talc

Talc is not particularly effective on its own as a tablet lubricant or glidant but very effective with lubricants in the role of an anti-adherent in that it effectively prevents sticking to surfaces. When using talc, it should always be blended into the formulation first followed by the lubricant (i.e.

magnesium stearate). The usable concentration of talc is in a range of 1-10%. Talc incompatible with quaternary ammonium compounds. It is not soluble in water.

(Freemantech, 2013)

1.12: Active pharmaceutical ingredients (API)

An active ingredient is the ingredient in a pharmaceutical drug that is biologically active. The similar terms active pharmaceutical ingredient (API) and bulk active are also used in medicine. Some medications may contain more than one active ingredient. The traditional word for the API is pharmacon or pharmakon (from Greek, adapted from pharmacos) which originally denoted a magical substance or drug.

1.12.1 Amlodipine

Amlodipine is a calcium channel blocker. They are very often used as anti-hypertensive agents besides their specific anti-ischemic use. At present Amlodipine has become the drug of choice in hypertension with or without cardiac ischemia because of the convenient dosage (once or twice daily) and absence of the possibility of reflex tachycardia or interference with the conductive system.

Mode of action: Contraction of the vascular smooth muscle is dependent on the intra-cellular free Ca++ (Calcium ions). The inhibition of transmural movement of Calcium ions decreases the total amount of intra-cellular Ca++and thereby causes relaxation of the arteriolar smooth muscles and decrease of peripheral resistance. The result is lowering of blood pressure.

Indication: These are ideal hypotensive in patients with bronchial asthma, diabetes mellitus, myocardial ischemia, impaired renal function. Moreover, these do not alter the serum lipids, glucose, uric acid or electrolytes.

Side-effects: Headache, Hushing, palpitation, tachycardia, dizziness are common side-effects. Sometimes, peripheral edema may also occur with Calcium-channel blockers.

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.

Contra indications: These drugs should not be used in cases of congestive cardiac failure or Sino-Atrial and Atrio-Ventricular blocks.

(Drugbank, 2005)

1.12.2: Propranolol

Propranolol is a sympatholytic nonselective beta blocker. It is used to treat high blood pressure; a number of heart dysrhythmias, thyrotoxicosis, and essential tremors. It is used to prevent migraine headaches, and to prevent further heart problems in those with angina or previous heart attacks. It comes in both oral and intravenous forms.

Mode of action: It works by slowing down the heart and decreasing the amount of blood it pumps out. This drug works by blocking the action of certain natural chemicals in your body

(such as epinephrine) that affect the heart and blood vessels. This effect reduces heart rate, blood pressure, and strain on the heart. Exactly how propranolol tablets works to treat migraines or tremors is not known.

Indications: This medication is a beta blocker used to treat high blood pressure, irregular heartbeats, shaking (tremors), and other conditions. It is used after a heart attack to improve the chance of survival. It is also used to prevent migraine headaches and chest pain (angina). Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. Preventing chest pain can help improve your ability to exercise.

Side effects: Cough producing mucus, difficulty with breathing tightness in the chest, chest pain or discomfort confusion about identity, place, and time congestion constipation, nausea etc.

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.

Contra indications: It should not be used in those with an already slow heart rate and most of those with heart failure. Quickly stopping the medication in those with coronary artery disease may worsen symptoms. It may worsen the symptoms of asthma. Common side effects include nausea, abdominal pain, and constipation. Greater care is recommended in those with liver or kidney problems. It may possibly cause harmful effects to the infant if taken during pregnancy.

(Drugbank, 2005)

Chapter two

Literature Review

2.1 Literature review

Around 80% of drug dosage forms is covered by solid dosage forms among all types of formulations, like tablet, capsules etc. Powder flow characteristic is one of the most important parameter to be checked in case of these dosage preparations. Flow ability of the formulations for the dosage forms, including both active pharmaceutical ingredients and powder excipients, is usually tested while the ingredients' flow by the research team. This flow characteristic determination of pharmaceutical ingredients has been continuing for many decades, and the researcher finally reached to a conclusion about using any ingredient, or benefits or problems of few ingredients together. Some of the studies are overviewed in the following of this review.

The antistatic properties of tablet lubricants such as magnesium stearate, polyethylene glycol 4000, sodium lauryl sulfate and talc was studied in nineteenth century by Gold and Palermo (Gold and Palermo, 1965). The data indicates that these lubricants have the ability to lower the accumulation of static charges which results the flow of material through a tablet hopper. The study showed that different highly static materials influence the antistatic properties of these lubricants. If the concentration of lubricant gets lower, the antistatic effectiveness is decreased.

Bolhuis and his research team studied on the flow and lubrication properties of a high dosage range drug, acetylsalicylic acid with different particle size distributions, which was formulated with directly compressible excipients and compressed into tablets in 1979 (Bolhuis, Lerk, Moes, 1979). 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 200C 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.

The effect of particle size on the compression mechanism and tensile strength of prepared tablets was determined in 1982 by 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 that experiment they found that declining the particle size of spray-dried lactose and Sta-Rx 1500 resulted in stronger compaction. Also the particle size variation of Avicel PH-101 did not showed any impact on tablet tensile strength. Their study was concluded by identifying a statement that angle of repose and Hausner ratio measurements indicated a connection between the internal forces of friction and cohesion of the different sized powders and the tensile strength of compacts formed from them.

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

In the same year in 1994 Schmidt and Rubensdorfer (Schmidt and Rubensdorfer, 1994) evaluated the powder characteristics and tableting properties of Ludipress which is a combination of povidone and crosspovidone. The scientists made a comparison with other binders. The study was to find out the flowability, bulk density, tapped density, Hausner ratio, angle of repose and particle size distribution in which morphological study were evaluated primarily. It has been stated that several samples of ludipress showed a good uniformity and flow characteristics than other excipients. The data was found by assessing the tableting parameters like crushing strength, friability and disintegration time.

The effect of eleven pharmaceutical excipients with Avicel PHI02 SCG was investigated by two scientists, Flemming and Mielck (Flemming and Mielck, 1995) in the next year. Physical characteristics like particle size distribution, true and bulk densities and flow rates had been

evaluated. The study yields, for micro-tableting purpose flow rates were calculated on modern high speed rotary tableting machine, and also from very narrow orifices.

In 1995 a journel was published (Juppo et al, 1995) about the compression of lactose glucose and mannitol granules. They show the effect of the amount of granulation liquid, compression speed and maximum compression force on the compressibility and compactibility of lactose, glucose and mannitol granules was studied. The porosity based on the geometrical shape and the uniformity of weight of tablets was also studied. Lactose and mannitol granules showed a greater compressibility than glucose granules. Mannitol granules produced the hardest tablets and lactose and glucose the weakest. All granule masses showed a relatively good continuous flow suitable for tablet production. Tablets compressed from lactose granules had the best uniformity of weight of the tablets studied.

While determining the angle of repose (AOR), cohesive and semi-cohesive powders have the tendency to block the funnel which makes it difficult to measure the AOR for these powders. In 1996, Ilse M. F. Wouters and Derek Geldart (Wouters andGeldart, 1996) did an experiment on 73 powders consisting of four materials including covering agents. The results showed that AOR of different combination increases with the decrease of mean particle size. AOR of these combinations were measured with the aerated bulk density which made this method a quick, sensitive and effective one for characterizing a wide range of powders.

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

In 1996, Gerald Gold, Ronald N. Duvall, Blaze T. Palermo and James G. Slater (Gold, et al., 1996) studied the effect of glidants on flow rate and angle of repose in drug formulation. They used fumed silicon dioxide, magnesium stearate, starch, and talc in combination with a set of selective materials. They had found that most glidants actually decreased the flow rate and glidants with lower AOR did not significantly increase the flow rate. However, they also suggested that for evaluating the flow rate of these materials, the AOR was not a reliable method.

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

In 1999, two scientists E.C. Abdullah and D. Geldart (Abdullah and Geldart, 1999) measured the bulk density of powders with two equipments to evaluate the flow property of porous and nonporous powders. The Hosokawa Powder Tester and the Copley Tap Density Volumeter were the two equipments. The Hosokawa Powder Tester gave accurate measurement of the aerated and tapped bulk densities due to the use of a fixed volume of powder and an accurately measured mass of powder. The Copley Tap Density Volumeter gave inaccurate measurements using a fixed mass of powder because it is difficult to measure the volume from the graduated cylinder. However, flow property of the powder increases with the increase of particle size though there is a critical particle size range above which flow property does not improve.

In the next 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.

Taylor and Ginsburg (Taylor and Ginsburg, 2000) measured flow property of powders by vibrating spatula, critical orifice, angle of repose, compressibility index and angle of repose. They found 72.4% variability in results and the results are not reproducible.

In 2000, FridrunPodczeck and Michael Newton (Podczeck and Newton, 2000) studied powder bulk properties and capsule filling performance on a tamp-filling machine with and without the addition of various concentrations of magnesium stearate. They found that the Carr's compressibility reaches its minimum value at 0.4% magnesium stearate. They suggested an improvement of powder flow in a mixture of powder containing lubricating agent compared to that of unlubricated material.

The next 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.

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

In 2002, a Chinese scientist, Anthony Chi-Ying Wong did an experiment on theangle of repose (AOR), tapped bulk densities (ρT), and aerated bulk densities (ρA) of 18 fractions of spherical glass beads which mean particle size was 12–190μm. It had been found that the ratio of angle of repose to aerated bulk densities was correlated with the ratio of aerated bulk densities to tapped bulk densities for free-flowing powder. Results of this experiment suggested that the ρA in the angle of repose can be replaced by ρT which will reduce the errors followed by the sensitivity of ρA.

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

In 2003, Yeli Zhang, Yuet Law and SibuChakrabarti (Zhang, Law and Chakrabarti, 2003) investigated the flowability of commonly used direct compression binders. Five classes of

excipients were evaluated, including microcrystalline cellulose (MCC), starch, lactose, dicalcium phosphate (DCP), and sugar. In general, the starch category exhibited the highest moisture. DCP displayed the highest density. MCC, starch, lactose, and sugar had shown moderate whereas DCP had shown excellent flowability).

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

Thalberg and two other researchers (Thalberg, Lindholm, Axelsson, 2004) compared flow characteristic of powders for inhalation in 2004. A series of placebo powders for inhalation was illustrated regarding bulk density and powder flowability using different techniques. The powders were prepared by mixing a pharmaceutical carrier grade of lactose with different fractions of intermediate sized and micronized lactose. A modified Hausner Ratio was attained by measurement of the bulkand the true densities. Other tests done were the angle of repose, the avalanching behaviour using the AeroFlow, and the yield strength using the uniaxial tester. Furthermore, the relation between ordered mixture composition and flowability was examined. The modified Hausner Ratio differentiates well between the investigated powders and seems to have the widest measuring range. It was also found that the poured and compressed bulk densities provide information about the packing of the particles in the powders. A good

correlation was obtained between the modified Hausner Ratio and the angle of repose. Regarding the powder composition, addition of micronized particles has a strong influence on the flowability of ordered mixtures, while intermediate sized particles have little impact on the powder flow.

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.

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

In 2005, Jun Yang and Ales Sliva (Yang, et al., 2005) indicated that surface-treated hydrophobic silica is more effective in improving the flowability of cornstarch particles than untreated hydrophilic silica.

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

Bagster and Crooks in 2006 (Bagster and Crooks, 2006) evaluated a number of methods of estimating flowability of some direct compression vehicles. There was little or no inter-relationship between angle of repose, compressibility and flow rate values. In addition, there was no correlation between any of these three values and tablet weight variation.

In 2010, Gerald Gold studied the commonly used glidants, fumed silicon dioxide, magnesium stearate, starch, and talc in combination with selected materials. Many of the more widely used glidants actually decreased the flow rate. Glidants which lowered the angle of repose did not necessarily increase the flow rate. Flow rate were not always detectable by angle of repose measurement. By doing the comparison of the angle of repose and the flow rate they suggested that the angle of repose was not a reliable method for evaluating the flow of these materials (Gold, et al., 2010).

In the year 2007 a study was conducted on flow property of co-processed particles of microcrystalline cellulose (MCC) and mannitol by Jacob and his research team (Jacob et al.,

2007 Both the excipients were fabricated by spray drying process to be used as a direct compression excipient in fast dissolving tablet formulation. The composite particles were examined for their powder and compression properties. The scientists observed that an increase in the MCC proportion imparted greater compressibility to the composite particles, but the flowability of these mixtures was decreased. Although MCC and mannitol have been widely used in the formulation of fast dissolving tablets, the non-wetting property of the hard compact central core may delay the disintegration time. Optimizing the ratio of mannitol and MCC in 1.25:1, the scientists found to have optimized powder and compressibility characteristics with fast sintegrating property (<15 s). It was concluded that a higher rate of powder flow can indirectly influence the rate of disintegration).

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

In 2008 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 2008, Rakhi Shah evaluated Angle of repose, bulk density, tapped density, Carr's compressibility index, and Hausner ratios of different grades of magnesium stearate powder. It was observed that the compendial methods were often non-discriminating for minor variations in powder flow. The additional characterization such as cohesivity, and caking strength were helpful in understanding the flow characteristics of pharmaceutical systems (Shah, et al., 2008).

In 2009, Erica Emerya and Jasmine Oliver evaluated the Hausner Ratio, the Carr Index, and the Angles of repose of Hydroxypropyl methylcellulose (HPMC). The flowability HPMC decreased with an increase in moisture content (Emerya, et al, 2009).

In 2010 Sarraguca and his team (Sarraguca¸ et al. 2010) established a new method for determining the physical properties of some pharmaceutical powders. The knowledge of their flow properties is of critical significance in operations such as blending,tablet compression, capsule filling, transportation, and in scale-up operations. Powders flow properties are measured using a number of parameters such as, angle of repose, compressibility index (Carr's index) and Hausner ratio. To estimate these properties, specific and expensive equipment with time-consuming analysis is required. They used near infrared spectroscopy is a fast and low-cost analytical technique. They determine the parameters associated with the flow properties of pharmaceutical powders, blended powders based on paracetamol as the active pharmaceutical ingredient were constructed in pilot scale. Spectra were recorded on a Fourier-transform near infrared spectrometer in reflectance mode. The parameters studied were the angle of repose, aerated and tapped bulk density. The correlation between the reference method values and the near infrared spectrum was performed by partial least squares and optimized in terms of latent variables using cross-validation. The near infrared based properties predictions were compared with the reference methods results. Prediction errors were varied between 2.35% for the angle of repose, 2.51% for the tapped density and 3.18% for the aerated density.

In 2013, Crouter and Briens (Crouter and Briens, 2013) investigated the flowability of MCC, HPMC, CMC, PVP, corn starch, and potato starch. Flowability of MCC, CMC and PVP

decreased after a critical moisture content and for corn starch, it was increased. Flowability of HPMC was not changed that much. The moisture decreased flowability by forming stronger interparticle liquid bridges and increased flowability by acting as a lubricant. The dynamic density of the celluloses and PVP decreased linearly with increasing moisture content as the particles swelled with water. The starches also swelled and decreased in dynamic density, but only after a moisture content corresponding to monolayer coverage of water around the particles had been reached.

In 2013, Silva and Splendor (Silva and Splendor, 2013) evaluated Bulk Density and Tapped Density of commonly used excipients according to European Pharmacopeia monograph (seventh edition) in order to study the influence of the procedure conditions. The results suggested that the leveling of the powder inside the cylinder ought to be avoided.

In 2013, Garett and Lauren (Garett and Lauren, 2013) investigated the effect of magnesium stearate, magnesium silicate, stearic acid, and calcium stearate on powder flowability. The Carr Index, and the Angles of repose were evaluated for those excipients. Of the tested lubricants, magnesium stearate provided the best increase in flowability even in the low amounts commonly added in formulations).

Another research in 2013 was done by Morin and Briens (Morin and Briens, 2013). They investigated the effect of lubricants on powder flowability as flowability into the tablet press is critical. Four lubricants (magnesium stearate, magnesium silicate, stearic acid, and calcium stearate) were mixed, in varying amounts, with spray-dried lactose. Among the tested lubricants, magnesium stearate increased the flowability most.

In recent years a work aimed to investigate the flowability properties of the basic powders used to make tablets by means of direct compression was made.Sallah and his team investigate in 2014. (Salleh et al, 2014) The main product in this study is Ficus deltoidea extract powder, while the excipients operated as binder were croscarmellose sodium (NaCMC or Acdisol) and microcrystalline cellulose (MCC or Avicel). The experimental results showed higher flow property values for binders compared with F. deltoidea extract powder. These results provide

essential information for the processing and handling of these powders during storage, transportation and also for the next processing step of powder – tabletting.

In the beginning of 2015 another literature published by Sawa and his team (Sawa et al, 2015) about flow properties relevant to the characterization, handling, and processing of powders. However, despite the automation of modern test equipment, it can be time consuming and expensive. In contrast, measurement of bulk density is straight forward and less laborious, and tapping devices are cheaper. They explore the relationship between Hausner ratio and cohesion and also examine correlation between Hausner ratio, σc/σy, and σ for a suite of 13 milled and 2 spray-dried lactose powders, 3 sand samples and 3 samples of refractory dust; Hausner ratio is the ratio of tapped bulk density to loose bulk density, σc is major consolidation stress, σy is unconfined yield stress and σpre is preconsolidation stress. Loose poured bulk density was measured following a modified New Zealand standard and tapped density measurement was based on a method for dry dairy products and the European Pharmacopoeia; Hausner ratio at 1250 taps was used. Their results show that cohesion at σ of 0.31 kPa, 0.61 kPa, 1.20 kPa, 2.41 kPa, and 4.85 kPa correlates linearly with Hausner ratio; the slope and intercept of the correlation are functions of σpre. These correlations are potentially useful for assessing flow characteristics when shear testing cannot be performed.

Chapter three

Materials and methods

3.1 API and excipient collection:

For the research purpose, we collected all the excipients from the different labs of East West University. The API we used (Amlodipine and Propranolol) we collected by our respected research supervisor Mr. Md. Anisur Rahman from ACI pharmaceutical limited.

3.2 List of excipient used:

All the excipients we used during this research program with their individual source (supplier) are listed below:

Table 3.1: List of excipients with their individual source

Serial no.	Name of excipients	Source (supplier name)
1.	Starch	MERK, Germany
2.	Poly ethylene glycol (PEG)	MERK, Germany
3.	Carboxy methyl cellulose (CMC)	MERK, Germany
4.	Mg stearate	MERK, Germany
5.	Talc	MERK, Germany

3.3 Equipment and instruments:

We used analytical balance only for weighting purpose. The suppliers of this equipment are SHIMADZU from Japan.

Fig 3.1: Analytical balance

3.4 Apparatus:

All the apparatus used in this research are listed below:

Table 3.2: Name of apparatus used

Serial no	Name of apparatus
1.	Beaker (100 ml)
2.	Test tubes with stands
3.	Measuring cylinder (50ml)
4.	Funnel
5.	Mortar pestle

6.	Spatula
7.	Stand
8.	Glass rod
9.	Aluminum foil paper
10.	Cling Wrap
11.	Scale
12.	White paper
13.	Masking tap

3.5 Methods

3.5.1 Preparation of Formulation sets of excipients:

Four sets of formulas were prepared by using different amounts of excipients and then the flow property of four formulas was determined by adding diluent. This had been purposely done to check whether the different amount of diluent in a particular formula somehow affects the existing formula, or not. All these four formulas contained all the group of excipients, generally used in a direct compressible tablet except the diluent. After adding diluent of different percentages the flow property of total excipient formulation was determined and then API was added with the formula. Then the flow property was determined again to observe the difference in flow ability of the formulation after adding API.

I weighed all the ingredients in analytical balance then mixed them uniformly by morter and pestle and placed into a properly cleaned dry test tube. A total of four sets of sample mixture of 3g were set up for further procedure that is the determination of flow property.

3.5.2 Preparation of formula 1 (F1)

Table 3.3: Amounts of excipients in formula one with justification

Formula	Excipients	Justification	Amount in the formula
Formula 1	Poly ethylene glycol	Binder	35%
	Carboxy methyl cellulose	Disintegrant	25%
	Mg stearate	Antiadherent	20%
	Talc	Lubricant	20%

Table 3.4: Calculation of excipients in 10gms of Formula- One

Ingredients	Amount in 10 gm
Poly ethylene glycol	3.5 gm
Carboxy methyl cellulose	2.5 gm
Mg stearate	2 gm
Talc	2 gm
	Total: 10 gm

After preparing 10g of F1, specific amount of diluent was mixed with a justified ratio. For this formula, starch was used. The required amount of both starch and F1 was calculated for

preparing each 3g of mixture in five different ratios. A total of five sets of sample mixture of 3g were set up for further procedure that is the determination of flow property.

Table: 3.5 Amount of starch and F1 in different ratio in 3g

Ratio	Starch: F1	Amount of starch:F1(in gm)
1	40% : 60%	1.2 : 1.8
2	45% : 55%	1.35 : 1.65
3	50% : 50%	1.65 : 1.35
4	55% : 45%	1.8 : 1.2
5	60% : 40%	1.5 : 1.5

3.5.3 Preparation of formula 2 (F2)

Table 3.6: Amounts of excipients in formula two with justification

Formula	Excipients	Justification	Amount in the formula
Formula 2	Poly ethylene glycol	Binder	35%
	Carboxy methyl cellulose	Disintegrant	25%
	Mg stearate	Antiadherent	20%
	Talc	Lubricant	20%

Table 3.7: Calculation of excipients in 10gms of Formula- two

Ingredients	Amount in 10 gm
Poly ethylene glycol	3.5 gm
Carboxy methyl cellulose	2.5 gm
Mg stearate	2 gm
Talc	2 gm
	Total: 10 gm

Unlike formula one the required amount of both starch and F2 was calculated for preparing each 3g of mixture in five different ratios. A total of five sets of sample mixture of 3g were set up for further procedure that is the determination of flow property.

Table: 3.8 Amount of starch and F2 in different ratio in 3g

Ratio	Starch: F2	Amount of starch:F2(in gm)
1	40% : 60%	1.2 : 1.8
2	47% : 53%	1.41 : 1.59
3	54% 46%	1.62 : 1.38
4	60% : 40%	1.8 : 1.2
5	65% : 35%	1.95 : 1.05

3.5.4 Preparation of formula 3

In formula three and four, the percentage of the excipients was changed but the excipients were the same. Then again 10 gm of formula without diluent was prepared and different ratio of diluent was mixed with that formula to give five sample mixtures of 3 gm.

Table 3.9: Amounts of excipients in formula three with justification

Formula	Excipients	Justification	Amount in the formula
Formula 3	Poly ethylene glycol	Binder	20%
	Carboxy methyl cellulose	Disintegrant	30%
	Mg stearate	Antiadherent	20%
	Talc	Lubricant	30%

Table 3.10: Calculation of excipients in 10gms of Formula- three

Ingredients	Amount in 10 gm
Poly ethylene glycol	2 gm
Carboxy methyl cellulose	3gm
Mg stearate	2 gm
Talc	3 gm
	Total: 10 gm

Table: 3.11 Amount of starch and F3 in different ratio in 3g

Ratio	Starch: F3	Amount of starch:F2(in gm)
1	30% : 70%	0.9 : 2.1
2	33% : 67%	0.99 : 2.01
3	36% 64%	1.08 : 1.92
4	39% : 61%	1.17 : 1.83
5	42% : 58%	1.26 : 1.74

3.5.5 Preparation of formula 4

Table 3.12: Amounts of excipients in formula four with justification

Formula	Excipients	Justification	Amount in the formula
Formula 3	Poly ethylene glycol	Binder	20%
	Carboxy methyl cellulose	Disintegrant	30%
	Mg stearate	Antiadherent	20%
	Talc	Lubricant	30%

Table 3.13: Calculation of excipients in 10gms of Formula- four

Ingredients	Amount in 10 gm
Poly ethylene glycol	2 gm
Carboxy methyl cellulose	3gm
Mg stearate	2 gm
Talc	3 gm
	Total: 10 gm

Table: 3.14: Amount of starch and F4 in different ratio in 3g

Ratio	Starch: F4	Amount of starch:F2(in gm)
1	45% : 55%	1.35 : 1.65
2	48% : 52%	1.44 : 1.56
3	52% : 48%	1.56 : 1.44
4	55% : 45%	1.65 : 1.35
5	58% : 42%	1.74 : 1.26

After that, active ingredients (amlodipine and propanolol) 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.

3.6 Flow property measurement

3.6.1 Determination of bulk volume:

- At first, uniformly mixed ingredients were transferred to a 50 ml measuring cylinder from the test tube.
- Then the measuring cylinder was tapped 2 times manually on a flat surface very gently. That was done to set all the powder on a vertical level.
- After that the height was measured by a scale and documented and that is the bulk volume.
- The same process was done five times and took the average of them to avoid errors and to get uniform data.

3.6.2 Determination of tapped volume:

- After taking the bulk volume, tapped volume was taken. At first, the measuring cylinder containing the mixtures of ingredient was tapped manually 50 times on a flat surface.]
- The tapping was achieved by raising the cylinder to a constant distance and then allowed to drop.
- The difference in the volume was observed and documented.
- The same process was done five times and took the average of them to find out the most acceptable data.

3.6.3 Determination of hausner's ratio and carr's index:

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

Compressibility index:

$$100 \times \frac{(true\ density - bulk\ density)}{true\ density}$$

Hausner ratio:

$$\frac{true\ density}{bulk\ density}$$

3.6.4 Measurement of Angle of repose:

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

- A funnel made up of plastic, glass or stainless steel was set with the holding stand tightly at first.
- The funnel was fixed in a place, 4 cm above the bench surface.
- Then a piece of clean white paper was placed on the bench surface.
- 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 white paper.
- After the cone from 3g of sample was built, height of the granules forming the cone (h) measured in cm and the radius (r) of the base in cm was measured by a scale.
- The angle of repose was calculated by the given formula and documented.
- The same process was run for five times and took the average of them to get the most acceptable data.

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

Chapter four

Result

4.1. Calculation of excipients formulation flow properties:

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

4.2.1 Formula 1:

Table 4.1: Values of the excipients formulation for determining Carr's index and Hausner's ratio for formula 1

Ratio	Bulk volume V_o(ml)	Most acceptable volume of V_o (ml)	Tapped volume Vr (ml)	Most acceptable volume of Vr (ml)	Housner ratio	Carr's index
Ratio 1	9.8	10.0	7.1	7.1	1.41	29.0
	10.0		7.2			
	9.5		7.4			
	9.8		7.5			
	10.0		7.1			
Ratio 2	9.6	9.8	7.0	7.0	1.4	28.57
	9.6		7.4			
	9.8		7.5			
	9.7		7.5			
	9.5		7.4			
Ratio 3	9.5	9.5	7.0	6.8	1.39	28.42
	9.0		7.2			
	9.5		7.2			
	9.5		6.8			
	9.2		7.0			

Ratio 4	9.0	9.0	6.8	6.5	1.38	27.77
	8.9		6.8			
	8.9		6.5			
	8.6		6.6			
	9.0		6.5			
Ratio 5	9.2	9.2	7.0	6.8	1.35	26.09
	8.8		6.8			
	8.6		7.1			
	8.8		7.1			
	8.6		7.0			

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

Table 4.2: Calculation of Angle of repose for formula 1

Ratio	Height (h) cm	Avg. Height (h) cm	Diameter (2r) cm	Avg. Diameter (2r)cm	Radius ®cm	Angle of Repose
Ratio 1	2.4	2.46	4.98	5.016	2.508	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	43.82
	2.38		5.02			
	2.42		4.88			
	2.36		4.96			
	2.35		4.9			
Ratio 3	2.35	2.36	5.2	5.11	2.55	42.74
	2.38		5.2			
	2.3		4.84			
	2.35		5.14			
	2.4		5.16			
Ratio 4	2.3	2.31	5.06	5.18	2.59	41.71
	2.35		5.22			
	2.3		5.14			
	2.25		5.22			
	2.35		5.28			
Ratio 5	2.22	2.24	5.32	5.26	2.63	40.44
	2.25		5.22			
	2.25		5.34			
	2.28		5.28			
	2.22		5.12			

4.2.2 Formula 1 with API (Amlodipine)

The flow property of Amlodipine was measured four individual formulations. The amount of API was measured compatible with the amount of our excipient formula then the flow property was measured from hausner's ratio, carr's index and angle of repose.

Table 4.3: Values of the excipients formulation with Amlodipine for determining Carr's index and Hausner's ratio for formula 1

Ratio	Bulk volume $V_{\circ}$(ml)	Most acceptable volume of $V_{\circ}$ (ml	Tapped volume Vr (ml)	Most acceptable volume of Vr (ml)	Housner ratio	Carr's index
Ratio 1	4.6	4.6	3.4	3.3	1.40	28.26
	4.6		3.3			
	4.5		3.3			
	4.55		3.3			
	4.5		3.4			
Ratio 2	4.55	4.55	3.4	3.3	1.38	27.47
	4.5		3.3			
	4.3		3.4			
	4.4		3.45			
	4.55		3.3			
Ratio 3	4.6	4.65	3.5	3.4	1.37	26.88
	4.65		3.4			
	4.6		3.3			
	4.55		3.5			
	4.5		3.4			

Ratio 4	4.5	4.55	3.4	3.35	1.35	26.37
	4.55		3.4			
	4.5		3.35			
	4.5		3.4			
	4.5		3.4			
Ratio 5	4.5	4.6	3.55	3.5	1.31	23.91
	4.55		3.5			
	4.5		3.5			
	4.5		3.55			
	4.6		3.5			

Table 4.4: Calculation of angle of repose for formula 1 with amlodipine

Ratio	Height (h)	Avg. Height (h)	Diameter (2r)	Avg. Diameter (2r)	Radius (r)	Angle of Repose
Ratio 1	1.1	1.15	2.4	2.40	1.20	43.78
	1.15		2.4			
	1.1		2.36			
	1.2		2.44			
	1.2		2.42			
Ratio 2	1.15	1.13	2.5	2.47	1.23	42.57
	1.15		2.52			
	1.10		2.4			
	1.15		2.49			
	1.1		2.42			
Ratio 3	1.2	1.18	2.72	2.65	1.32	41.79
	1.2		2.6			
	1.15		2.62			
	1.15		2.7			
	1.2		2.6			
Ratio 4	1.1	1.12	2.6	2.65	1.33	40.10
	1.1		2.62			
	1.15		2.68			
	1.15		2.72			
	1.1		2.64			
Ratio 5	1.1	1.04	2.6	2.56	1.28	39.09
	1.0		2.5			
	1.1		2.7			
	1.0		2.48			
	1.0		2.54			

4.2.3 Formula 1 with API (Propranolol)

Table 4.5: Values of the excipients formulation with Propranolol for determining Carr's index and Hausner's ratio for formula 1

Ratio	Bulk volume $V_{\circ}$(ml)	Most acceptable volume of $V_{\circ}$ (ml	Tapped volume Vr (ml)	Most acceptable volume of Vr (ml)	Housner ratio	Carr's index
Ratio 1	4.5	4.55	3.4	3.3	1.38	27.47
	4.45		3.5			
	4.5		3.3			
	4.55		3.4			
	4.5		3.35			
Ratio 2	4.55	4.6	3.35	3.35	1.37	27.17
	4.6		3.4			
	4.5		3.45			
	4.6		3.35			
	4.5		3.4			
Ratio 3	4.5	4.55	3.4	3.35	1.36	26.37
	4.55		3.5			
	4.55		3.4			
	4.45		3.35			
	4.5		3.45			
Ratio 4	4.45	4.5	3.35	3.35	1.34	25.55
	4.5		3.4			
	4.5		3.4			
	4.5		3.45			
	4.45		3.35			

Ratio 5	4.40	4.4	3.5	3.3	1.3	25
	4.40		3.4			
	4.35		3.4			
	4.3		3.3			
	4.4		3.3			

Table 4.6: Calculation of angle of repose for formula 1 with propranolol

Ratio	Height (h)	Avg. Height (h)	Diameter (2r)	Avg. Diameter (2r)	Radius (r)	Angle of Repose
Ratio 1	1.15	1.13	2.38	2.41	1.2	43.28
	1.15		2.34			
	1.1		2.43			
	1.15		2.40			
	1.1		2.50			
Ratio 2	1.1	1.1	2.3	2.36	1.18	42.99
	1.1		2.42			
	1.15		2.36			
	1.1		2.46			
	1.05		2.24			
Ratio 3	1.1	1.12	2.44	2.44	1.22	42.55
	1.15		2.54			
	1.15		2.45			
	1.1		2.42			
	1.1		2.34			
Ratio 4	1.0	1.04	2.22	2.33	1.16	41.87
	1.0		2.27			
	1.1		2.35			
	1.0		2.48			
	1.1		2.34			
Ratio 5	1.0	1.02	2.32	2.41	1.21	40.13
	1.05		2.45			
	1.05		2.55			
	1.0		2.48			
	1.0		2.24			

4.2.4 Comparison between the ratios of three formulas in graph for F1

4.2.4.1: Hausner's ratio:

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

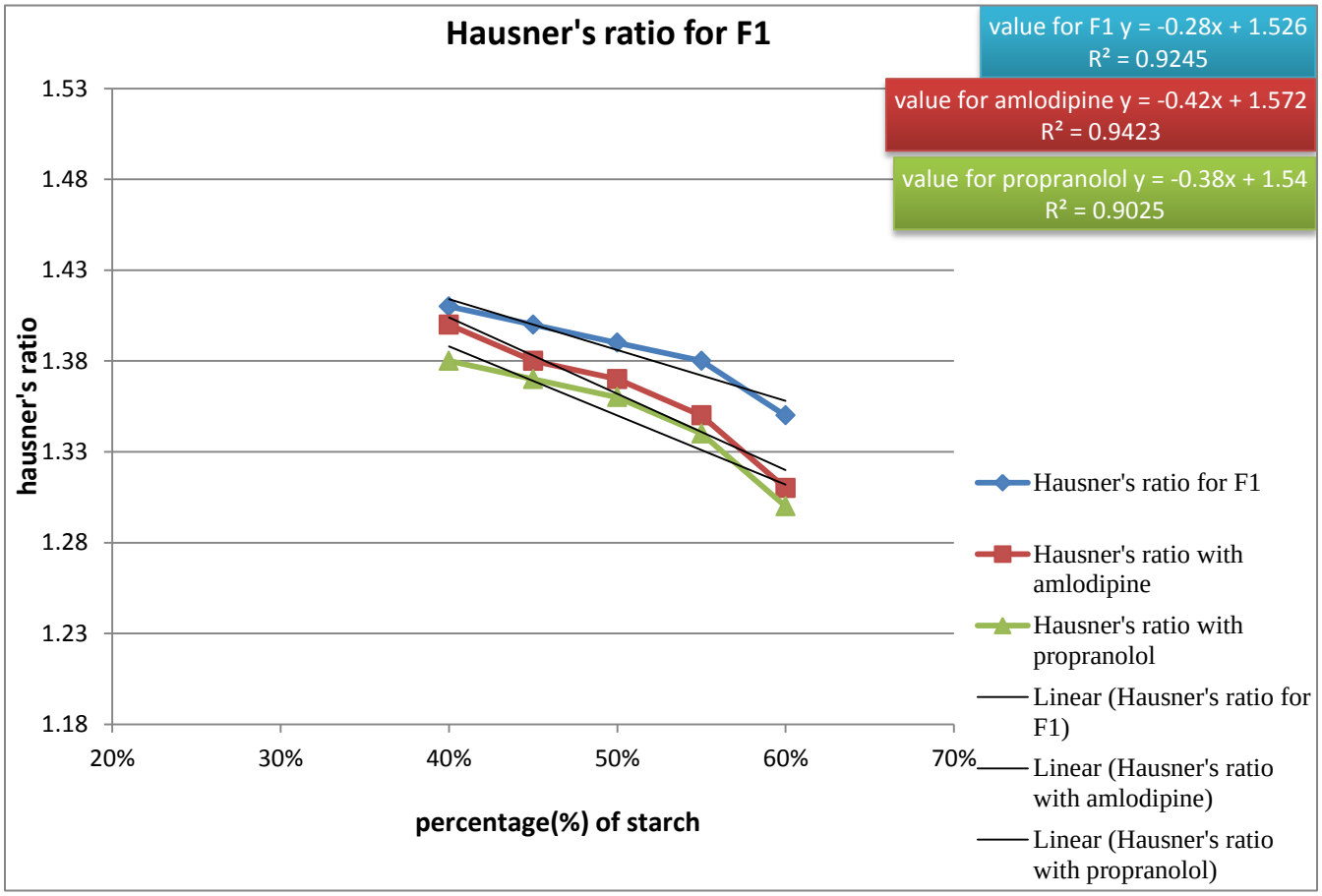

Figure 4.1: A percentage ratio of starch versus Hausner's ratio graph F1

4.2.4.2: Carr's index

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

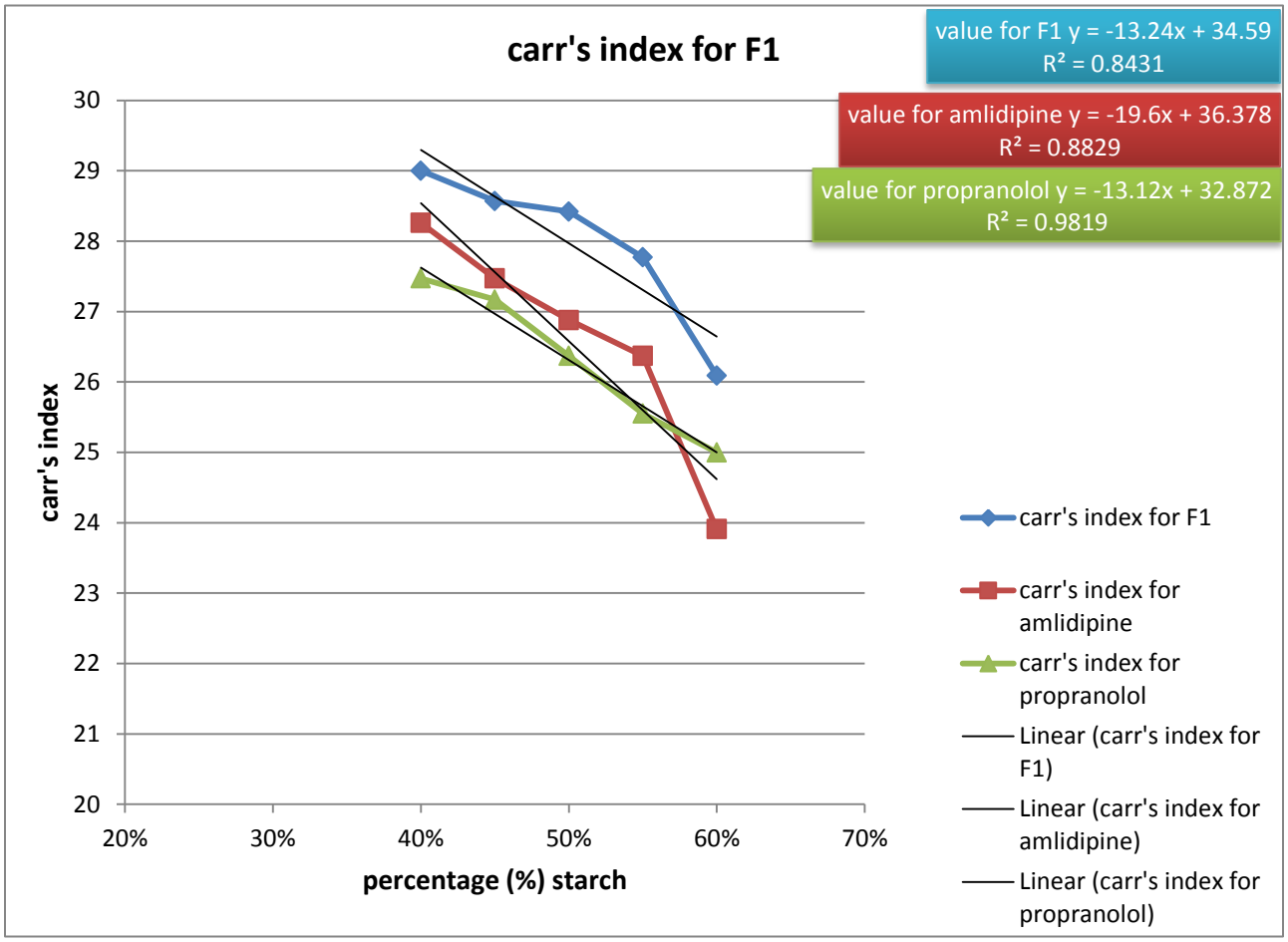

Figure 4.2: A percentage ratio of starch versus Carr's index graph F1

4.2.4.3: Angle of repose

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

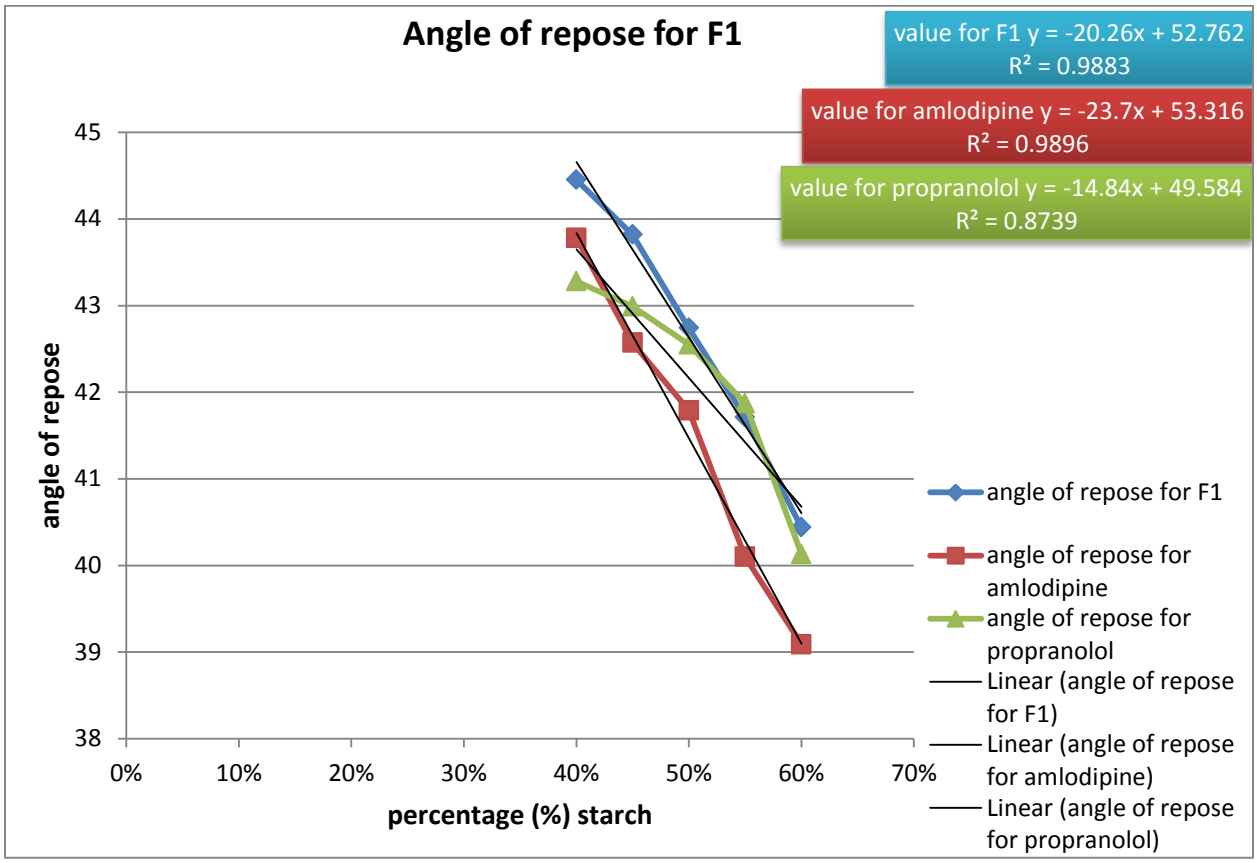

Figure 4.3: A percentage ratio of starch versus angle of repose graph F1

4.3.1: Formula 2: The ratios of excipients were the same but the percentage of starch was varied in formula 2.

Table 4.7: Values of individual excipients for determining Carr's index and Hausner's ratio for formula 2

Ratio	Bulk volume $V_{\circ}$(ml)	Most acceptable volume of $V_{\circ}$ (ml	Tapped volume Vr (ml)	Most acceptable volume of Vr (ml)	Housner ratio	Carr's index
Ratio 1	8.2	8.5	6.8	6.4	1.33	24.71
	8.5		6.5			
	8.2		6.4			
	8.4		6.5			
	8.1		6.4			
Ratio 2	8.1	8.1	6.3	6.2	1.31	23.46
	7.8		6.2			
	8.1		6.6			
	8.1		6.5			
	8.0		6.8			
Ratio 3	7.8	7.8	6.4	6.05	1.29	22.44
	7.5		6.2			
	7.6		6.1			
	7.8		6.05			
	7.5		6.1			
Ratio 4	7.0	7.5	6.1	6.0	1.25	20
	7.5		6.0			
	7.2		6.1			
	7.5		6.4			
	7.2		6.3			

Ratio 5	7.2	7.2	6.0	5.9	1.22	18
	7.0		5.9			
	7.1		6.1			
	7.0		6.0			
	6.8		5.9			

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

Table 4.8: Calculation of Angle of repose for formula 2

Ratio	Height (h)cm	Avg. Height (h)cm	Diameter (2r)cm	Avg. Diameter (2r)cm	Radius (r)cm	Angle of Repose
Ratio 1	1.9	1.99	4.68	4.73	2.37	40.02
	1.95		4.74			
	1.94		4.78			
	1.95		4.76			
	1.95		4.7			
Ratio 2	1.85	1.82	4.88	4.67	2.35	37.75
	1.85		4.64			
	1.8		4.64			
	1.82		4.6			
	1.8		4.72			
Ratio 3	1.7	1.72	4.59	4.59	2.29	36.91
	1.7		4.56			
	1.74		4.58			
	1.75		4.68			
	1.7		4.52			
Ratio 4	1.65	1.62	4.64	4.56	2.28	34.39
	1.59		4.6			
	1.6		4.48			
	1.65		4.54			
	1.6		4.54			
Ratio 5	1.5	1.54	4.5	4.62	2.31	33.69
	1.6		4.72			
	1.55		4.48			
	1.55		4.68			
	1.5		4.72			

4.3.2: Formula 2 with API (Amlodipine):

Table 4.9: Values of the excipients formulation with amlodipine for determining Carr's index and Hausner's ratio for formula 2

Ratio	Bulk volume V_o(ml)	Most acceptable volume of V_o (ml	Tapped volume Vr (ml)	Most acceptable volume of Vr (ml)	Housner ratio	Carr's index
Ratio 1	4.8	4.9	3.8	3.7	1.32	24.89
	4.8		3.8			
	4.9		3.7			
	4.7		3.9			
	4.9		3.7			
Ratio 2	5.0	5.0	4.0	3.85	1.30	23
	5.0		3.85			
	4.9		3.9			
	4.8		3.9			
	4.9		3.9			
Ratio 3	4.9	5.0	4.1	3.9	1.28	22
	5.0		3.9			
	4.8		4.0			
	5.0		4.0			
	4.9		4.0			
Ratio 4	4.8	4.8	3.9	3.85	1.25	19.8
	4.8		3.9			
	4.8		4.0			
	4.6		3.85			
	4.7		4.0			

Ratio 5	4.6	4.9	4.2	4.0	1.23	18.37
	4.6		4.0			
	4.8		4.1			
	4.9		4.1			
	4.9		4.0			

Table 4.10: Calculation of Angle of repose for formula 2 with amlodipine

Ratio	Height (h)	Avg. Height (h)	Diameter (2r)	Avg. Diameter (2r)	Radius (r)	Angle of Repose
Ratio 1	1.15	1.17	2.86	2.94	1.47	38.52
	1.15		2.84			
	1.15		2.94			
	1.2		3.0			
	1.2		3.08			
Ratio 2	1.1	1.06	2.98	2.81	1.40	37.13
	1.1		2.9			
	1.1		2.88			
	1.0		2.6			
	1.0		2.68			
Ratio 3	1.1	1.14	3.12	3.19	1.6	35.47
	1.1		3.1			
	1.2		3.36			
	1.1		3.06			
	1.2		3.32			
Ratio 4	1.1	1.12	3.22	3.25	1.63	34.49
	1.1		3.14			
	1.15		3.34			
	1.15		3.36			
	1.1		3.2			
Ratio 5	1.0	0.96	3.1	2.98	1.49	32.79
	0.9		2.8			
	0.9		2.82			
	1.0		3.1			
	1.0		3.08			

4.3.3: Formula 2 with API (Propranolol):

Table 4.11: Values of the excipients formulation with Propranolol for determining Carr's index and Hausner's ratio for formula 2

Ratio	Height (h)	Avg. Height (h)	Diameter (2r)	Avg. Diameter (2r)	Radius (r)	Angle of Repose
Ratio 1	4.8	4.85	3.65	3.65	1.33	24.74
	4.85		3.7			
	4.85		3.75			
	4.75		3.7			
	4.8		3.65			
Ratio 2	4.9	5.0	3.8	3.8	1.31	24
	5.0		3.8			
	4.95		3.8			
	5.0		3.85			
	4.9		3.85			
Ratio 3	4.9	4.95	3.9	3.9	1.27	21.21
	4.9		4.0			
	4.8		3.9			
	4.95		3.9			
	4.95		4.0			
Ratio 4	4.8	4.8	3.9	3.85	1.25	19.8
	4.7		3.85			
	4.7		3.85			
	4.8		3.9			
	4.8		3.9			

Ratio 5	4.85	4.85	4.0	3.9	1.23	19.59
	4.75		4.0			
	4.8		3.9			
	4.8		4.0			
	4.85		3.9			

Table 4.12: Calculation of Angle of repose for formula 2 with propranolol

Ratio	Height (h)	Avg. Height (h)	Diameter (2r)	Avg. Diameter (2r)	Radius (r)	Angle of Repose
Ratio 1	1.15	1.16	2.92	2.87	1.44	38.85
	1.2		2.8			
	1.2		2.86			
	1.15		2.86			
	1.15		2.9			
Ratio 2	1.15	1.08	2.88	2.8	1.4	37.65
	1.1		2.91			
	1.1		2.87			
	1.0		2.66			
	1.05		2.68			
Ratio 3	1.05	1.13	3.06	3.19	1.6	35.23
	1.1		3.16			
	1.1		3.3			
	1.2		3.22			
	1.2		3.21			
Ratio 4	1.1	1.11	3.26	3.22	1.61	34.58
	1.1		3.22			
	1.05		3.2			
	1.15		3.02			
	1.15		3.38			
Ratio 5	1.05	0.97	3.18	3.08	1.54	32.21
	1.0		3.07			
	0.9		2.84			
	1.0		3.18			
	0.9		3.14			

4.3.4: Comparison between the ratios of three formulas in graph for F2

4.3.4.1: Hausner's ratio

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

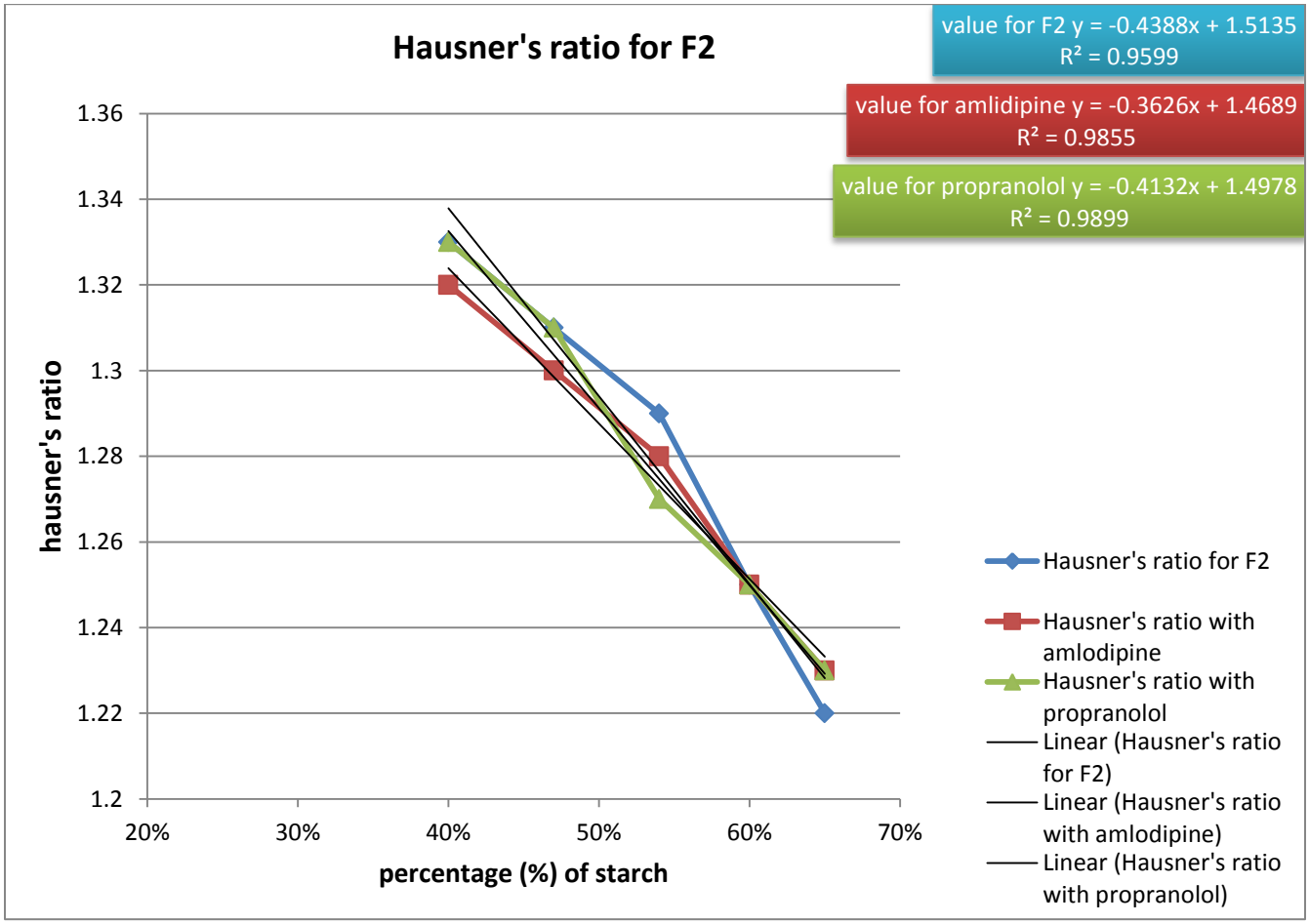

Figure 4.4: A percentage ratio of starch versus Hausner's ratio graph for F2

4.3.4.2: Carr's index

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

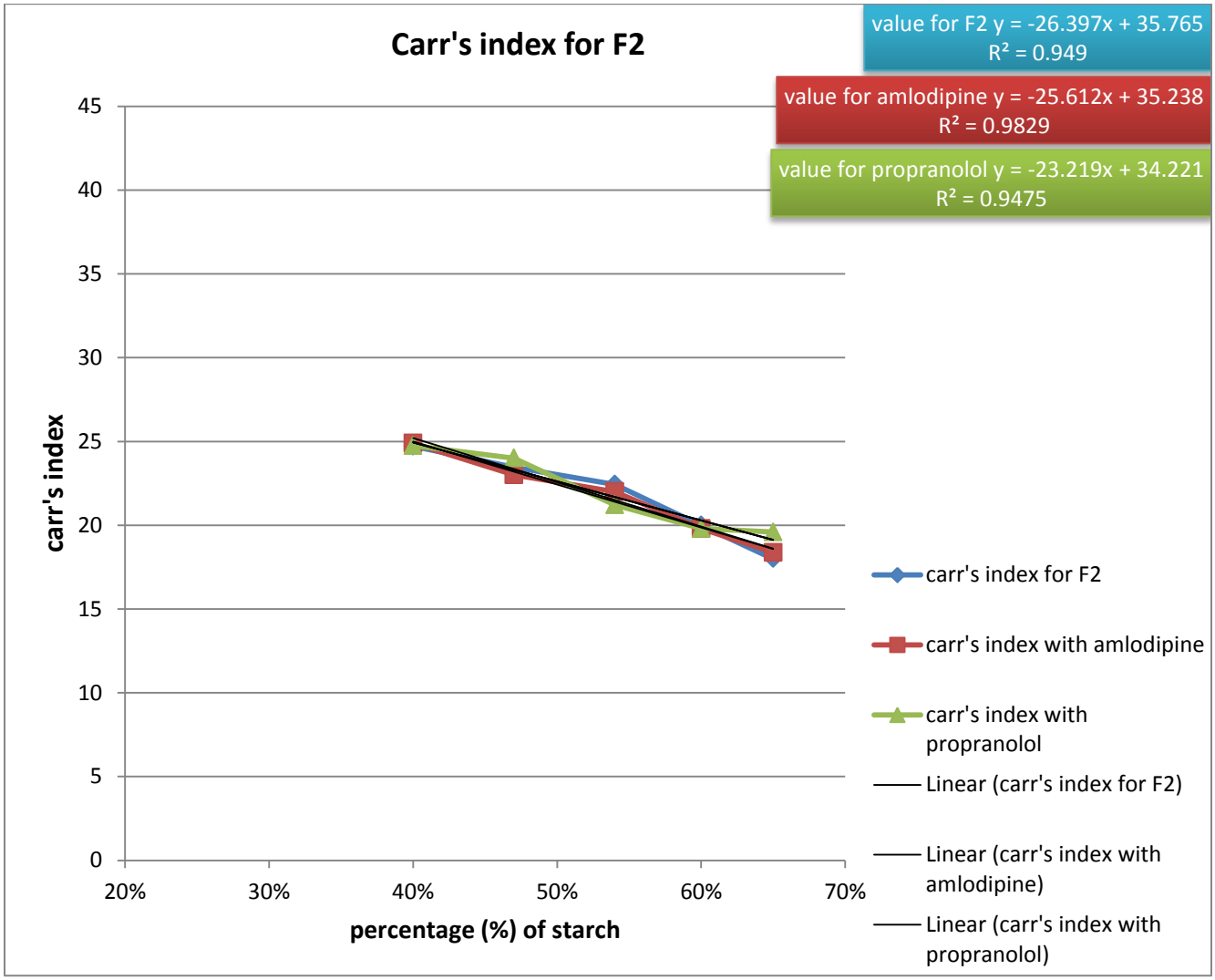

Figure 4.5: A percentage ratio of starch versus Carr's index graph for F2

4.3.4.3: Angle of repose

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

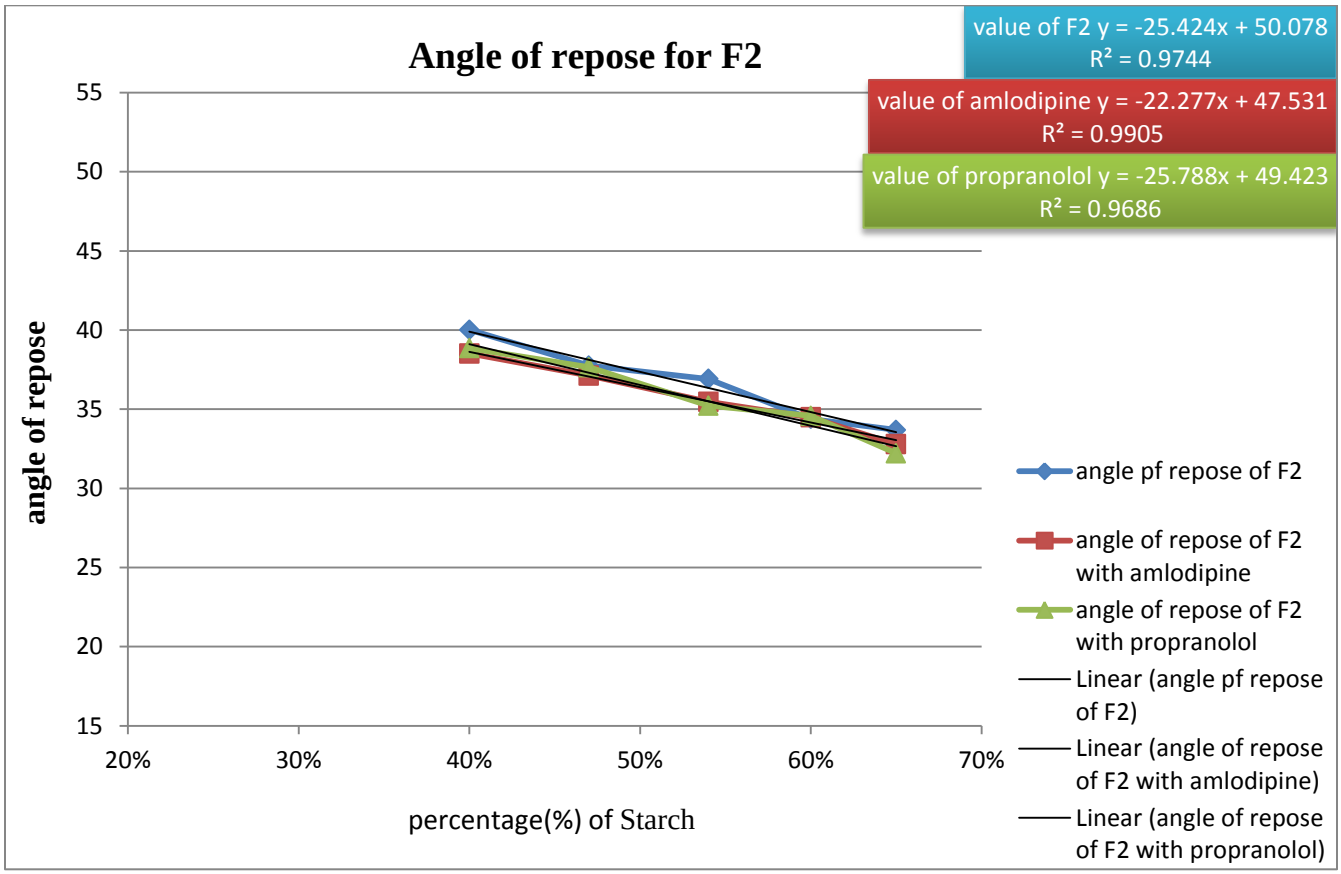

Figure 4.6: A percentage ratio of starch versus angle of repose graph for F2

4.4.1: Formula 3: Here the ratio of the excipients in the formula and the percentage of starch both were changed. Percentage of binder was reduced to get better flow property.

Table 4.13: Values of excipient formulation for determining Carr's index and Hausner's ratio for formula 3

Ratio	Bulk volume $V_{\circ}$(ml)	Most acceptable volume of $V_{\circ}$ (ml	Tapped volume Vr (ml)	Most acceptable volume of Vr (ml)	Housner ratio	Carr's index
Ratio 1	7.6	7.6	6.3	6.1	1.25	19.74
	7.5		6.1			
	7.6		6.2			
	7.4		6.4			
	7.4		6.4			
Ratio 2	7.2	7.4	6.1	6.1	1.21	17.57
	7.2		6.1			
	7.0		6.2			
	7.4		6.2			
	7.4		6.3			
Ratio 3	7.4	7.5	6.3	6.25	1.20	16.67
	7.5		6.4			
	7.0		6.25			
	7.5		6.3			
	7.2		6.25			
Ratio 4	7.0	7.2	6.5	6.2	1.17	13.88
	7.2		6.3			
	7.0		6.5			
	7.1		6.2			
	7.2		6.5			

Ratio 5	7.0	7.0	6.2	6.1	1.15	12.86
	6.9		6.5			
	6.8		6.2			
	7.0		6.1			
	6.9		6.1			

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

4.14: Table: Calculation of Angle of repose for formula 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	1.62	4.24	4.28	2.14	37.13
	1.6		4.36			
	1.65		4.28			
	1.65		4.3			
	1.6		4.22			
Ratio 2	1.55	1.56	4.42	4.31	2.16	35.90
	1.6		4.28			
	1.6		4.28			
	1.55		4.27			
	1.55		4.3			
Ratio 3	1.5	1.57	4.35	4.53	2.26	34.74
	1.6		4.6			
	1.6		4.62			
	1.6		4.7			
	1.55		4.67			
Ratio 4	1.6	1.56	4.96	4.79	2.4	33.08
	1.6		4.67			
	1.5		4.7			
	1.5		4.65			
	1.6		4.96			
Ratio 5	1.5	1.48	4.8	4.88	2.44	31.24
	1.5		4.92			
	1.4		4.78			
	1.4		4.7			
	1.6		5.2			

4.4.2: Formula 3 with API (Amlodipine):

Table 4.15: Values of the excipients formulation with amlodipine for determining Carr's index and Hausner's ratio for formula 3

Ratio	Bulk volume $V_{\circ}$(ml)	Most acceptable volume of $V_{\circ}$ (ml	Tapped volume Vr (ml)	Most acceptable volume of Vr (ml)	Housner ratio	Carr's index
Ratio 1	4.7	4.8	4.0	3.9	1.23	18.75
	4.7		3.9			
	4.8		4.1			
	4.7		4.1			
	4.8		3.9			
Ratio 2	4.8	5.0	4.3	4.1	1.22	18
	4.8		4.1			
	4.9		4.1			
	5.0		4.2			
	5.0		4.2			
Ratio 3	5.0	5.1	4.4	4.3	1.19	15.69
	4.9		4.3			
	5.1		4.4			
	5.0		4.5			
	5.0		4.5			
Ratio 4	4.8	4.95	4.3	4.25	1.16	14.14
	4.95		4.25			
	4.8		4.3			
	4.9		4.3			
	4.7		4.25			

Ratio 5	5.0	5.0	4.4	4.35	1.15	13
	5.0		4.4			
	4.9		4.4			
	4.8		4.35			
	5.0		4.6			

4.16: Table: Calculation of Angle of repose for formula 3 with amlodipine

Ratio	Height (h)	Avg. Height (h)	Diameter (2r)	Avg. Diameter (2r)	Radius (r)	Angle of Repose
Ratio 1	0.95	0.93	2.48	2.44	1.22	37.32
	0.90		2.36			
	1.0		2.62			
	0.90		2.38			
	0.90		2.34			
Ratio 2	0.95	0.98	2.6	2.66	1.33	36.38
	1.0		2.7			
	1.0		2.74			
	0.95		2.54			
	1.0		2.7			
Ratio 3	1.0	0.99	2.7	2.79	1.4	35.27
	1.0		2.88			
	1.0		2.76			
	0.95		2.7			
	1.0		2.92			
Ratio 4	0.9	0.91	2.76	2.8	1.4	33.02
	0.9		2.7			
	0.9		2.7			
	0.95		2.96			
	0.9		2.86			
Ratio 5	0.8	0.83	2.7	2.83	1.42	30.31
	0.8		2.72			
	0.9		3.0			
	0.85		2.88			
	0.8		2.86			

4.4.3: Formula 3 with API (Propranolol):

Table 4.17: Values of the excipients formulation with Propranolol for determining Carr's index and Hausner's ratio for formula 3

Ratio	Bulk volume $V_{\circ}$(ml)	Most acceptable volume of $V_{\circ}$ (ml	Tapped volume Vr (ml)	Most acceptable volume of Vr (ml)	Housner ratio	Carr's index
Ratio 1	4.8	4.85	4.1	4.0	1.24	19.59
	4.8		4.15			
	4.85		4.1			
	4.85		4.0			
	4.8		4.0			
Ratio 2	4.95	4.95	4.0	4.0	1.23	19.19
	4.9		4.1			
	4.9		4.15			
	4.85		4.15			
	4.9		4.1			
Ratio 3	5.0	5.1	4.2	4.2	1.2	17.65
	5.1		4.25			
	5.1		4.2			
	5.1		4.25			
	5.0		4.3			
Ratio 4	4.9	4.9	4.3	4.2	1.17	14.29
	4.8		4.2			
	4.85		4.2			
	4.8		4.3			
	4.9		4.2			

Ratio 5	5.0	5.0	4.45	4.35	1.15	13
	4.9		4.4			
	4.9		4.4			
	4.9		4.35			
	5.0		4.4			

4.18: Table: Calculation of Angle of repose for formula 3 with propranolol

Ratio	Height (h)	Avg. Height (h)	Diameter (2r)	Avg. Diameter (2r)	Radius (r)	Angle of Repose
Ratio 1	0.95	0.98	2.45	2.53	1.27	37.66
	1.0		2.66			
	1.0		2.56			
	1.0		2.55			
	0.95		2.44			
Ratio 2	0.95	0.97	2.64	2.64	1.32	36.31
	0.95		2.54			
	0.95		2.58			
	1.0		2.72			
	1.0		2.74			
Ratio3	1.0	0.97	2.83	2.73	1.37	35.58
	0.95		2.56			
	0.95		2.72			
	1.0		2.86			
	1.0		2.7			
Ratio 4	0.9	0.94	2.77	2.83	1.41	33.69
	0.95		2.8			
	0.9		2.86			
	0.95		2.9			
	1.0		2.8			
Ratio 5	0.9	0.91	2.98	2.89	1.44	32.30
	0.95		2.92			
	0.85		2.84			
	0.9		2.88			
	0.95		2.92			

4.4.4: Comparison between the ratios of three formulas in graph for F3

4.4.4.1: Hausner's ratio:

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

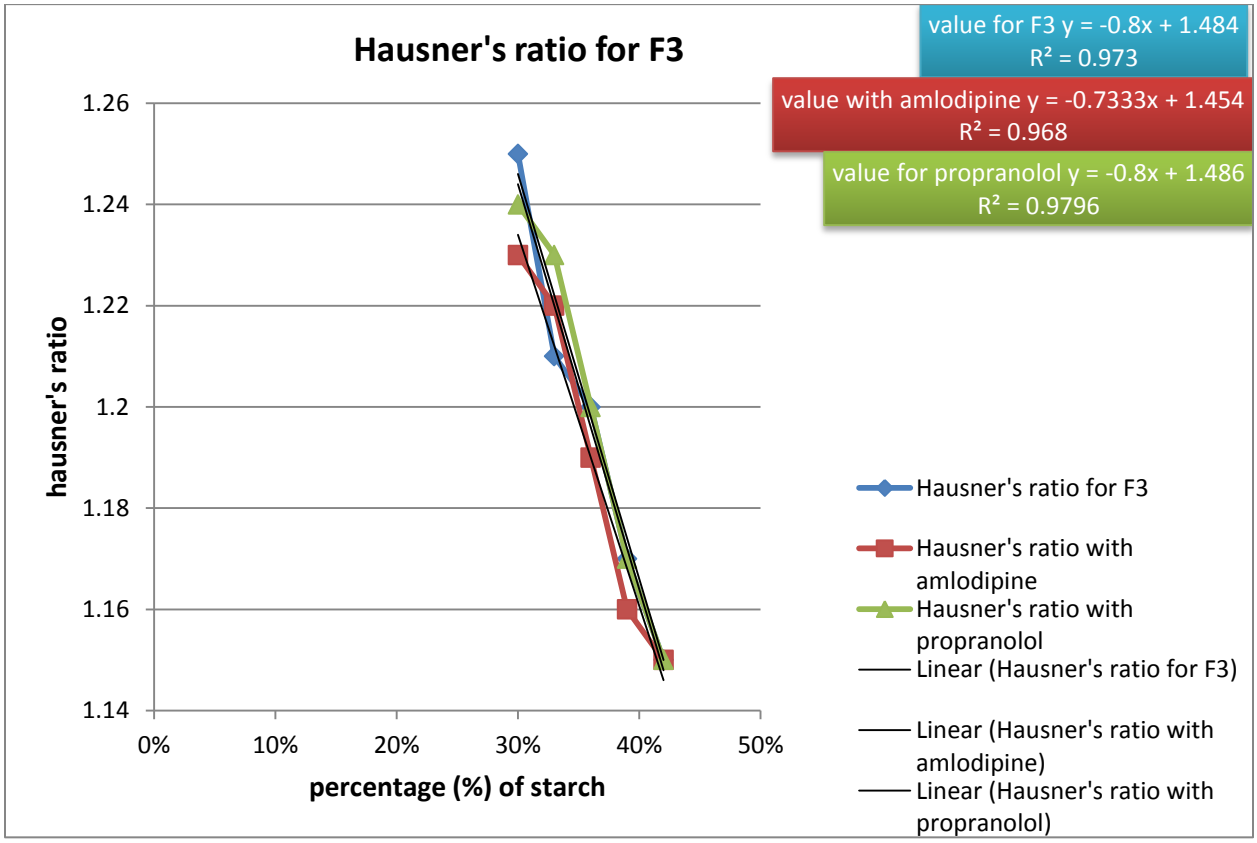

Figure 4.7: A percentage ratio of starch versus Hausner's ratio graph for F3

4.4.4.2: Carr's index:

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

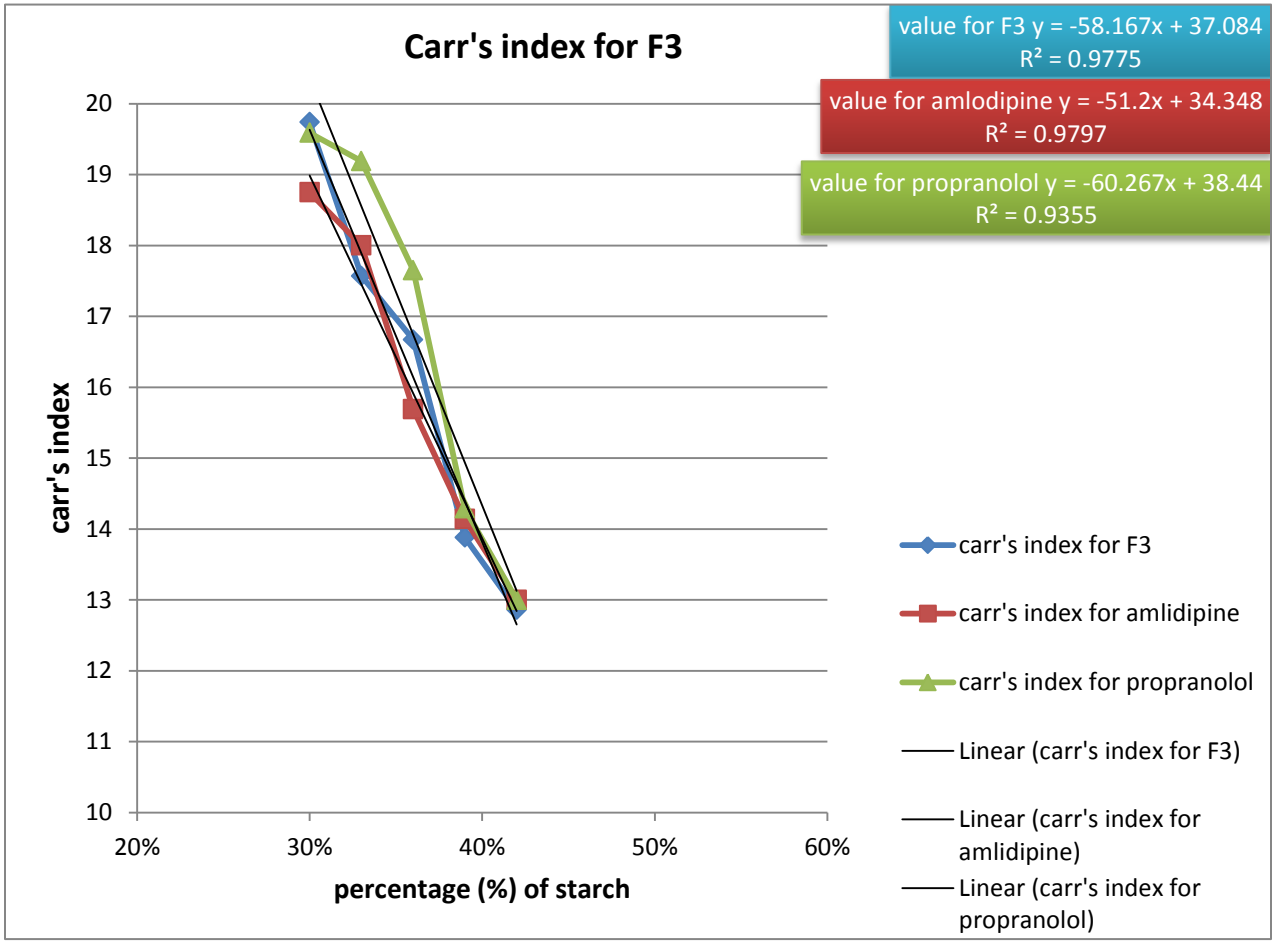

Figure 4.8: A percentage ratio of starch versus Carr's index graph for F3

4.4.4.3: Angle of repose:

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

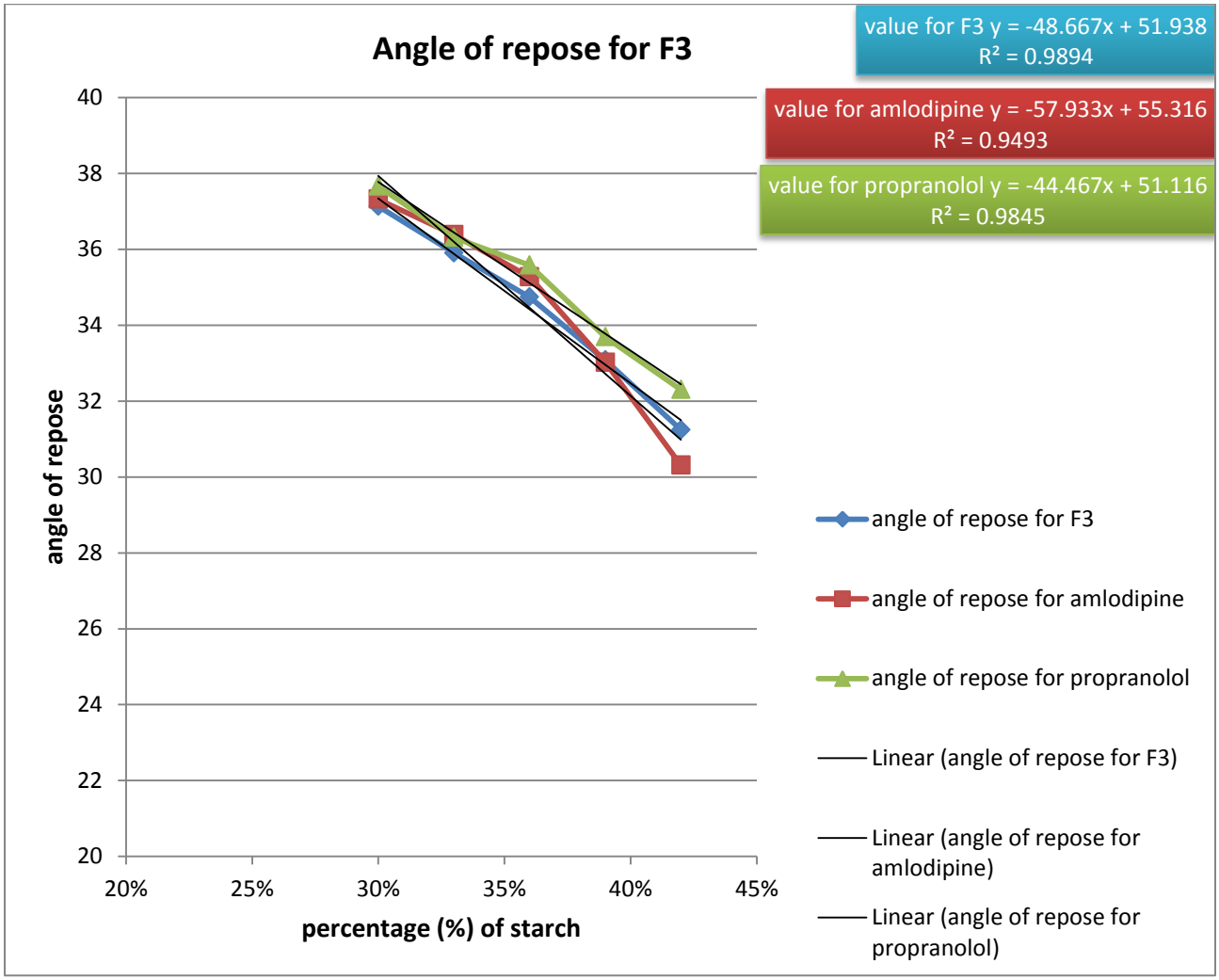

Figure 4.9: A percentage ratio of starch versus angle of repose graph for F3

4.5.1: Formula 4: Here the ratio of the excipients in the formula and the percentage of starch both were same as formula 3.

Table 4.19: Values of individual excipients for determining Carr's index and Hausner's ratio for formula 4

Ratio	Bulk volume $V_{\circ}$(ml)	Most acceptable volume of $V_{\circ}$ (ml	Tapped volume Vr (ml)	Most acceptable volume of Vr (ml)	Housner ratio	Carr's index
Ratio 1	7.0	7.1	5.9	5.9	1.20	16.90
	7.1		6.1			
	7.0		6.0			
	7.0		6.1			
	7.1		5.9			
Ratio 2	7.1	7.2	6.2	6.1	1.18	15.28
	7.2		6.1			
	7.2		6.1			
	7.2		6.2			
	7.0		6.3			
Ratio 3	7.0	7.0	6.2	6.0	1.16	14.29
	6.9		6.2			
	7.0		6.2			
	7.0		6.0			
	6.9		6.0			
Ratio 4	7.0	7.0	6.1	6.1	1.15	12.85
	7.0		6.2			
	6.9		6.1			
	7.0		6.1			
	6.9		6.2			

Ratio 5	6.9	7.1	6.3	6.3	1.13	11.27
	7.0		6.3			
	6.9		6.4			
	7.1		6.4			
	7.1		6.3			

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

4.20: Table: Calculation of Angle of repose for formula 4

Ratio	Height (h)cm	Avg. Height (h)cm	Diameter (2r)cm	Avg. Diameter (2r)cm	Radius (r)cm	Angle of Repose
Ratio 1	1.7	1.65	4.55	4.77	2.24	36.38
	1.6		4.34			
	1.7		4.56			
	1.6		4.53			
	1.65		4.4			
Ratio 2	1.6	1.62	4.4	4.59	2.3	35.16
	1.6		4.67			
	1.65		4.68			
	1.6		4.58			
	1.65		4.6			
Ratio 3	1.5	1.56	4.5	4.7	2.35	33.58
	1.5		4.94			
	1.65		4.76			
	1.6		4.7			
	1.55		4.6			
Ratio 4	1.4	1.49	4.65	4.88	2.44	31.41
	1.5		5.1			
	1.4		4.65			
	1.6		5.2			
	1.55		4.8			
Ratio 5	1.4	1.44	4.9	5.0	2.5	29.94
	1.5		5.16			
	1.4		4.8			
	1.5		5.25			
	1.4		4.9			

4.5.2: Formula 4 with API (Amlodipine):

Table 4.21: Values of the excipients formulation with amlodipine for determining Carr's index and Hausner's ratio for formula 4

Ratio	Bulk volume $V_{\circ}$(ml)	Most acceptable volume of $V_{\circ}$ (ml	Tapped volume Vr (ml)	Most acceptable volume of Vr (ml)	Housner ratio	Carr's index
Ratio 1	4.6	4.8	4.0	4.0	1.2	16.67
	4.8		4.1			
	4.8		4.1			
	4.7		4.0			
	4.8		4.1			
Ratio 2	4.6	4.8	4.1	4.1	1.17	14.58
	4.8		4.2			
	4.5		4.2			
	4.6		4.1			
	4.8		4.3			
Ratio 3	4.7	4.9	4.2	4.2	1.16	14.29
	4.9		4.3			
	4.8		4.4			
	4.7		4.2			
	4.8		4.4			
Ratio 4	4.7	4.7	4.3	4.1	1.14	12.77
	4.7		4.4			
	4.6		4.1			
	4.7		4.3			
	4.6		4.1			

Ratio 5	4.6	4.7	4.2	4.2	1.12	10.64
	4.7		4.3			
	4.7		4.3			
	4.6		4.3			
	4.5		4.2			

Table 4.22: Calculation of Angle of repose for formula 4 with amlodipine

Ratio	Height (h)	Avg. Height (h)	Diameter (2r)	Avg. Diameter (2r)	Radius (r)	Angle of Repose
Ratio 1	0.9	0.89	2.5	2.5	1.25	35.45
	0.9		2.62			
	0.85		2.44			
	0.9		2.48			
	0.9		2.44			
Ratio 2	0.8	0.82	2.40	2.46	1.23	33.65
	0.8		2.4			
	0.85		2.58			
	0.80		2.52			
	0.85		2.42			
Ratio 3	0.80	0.82	2.49	2.52	1.26	33.05
	0.80		2.45			
	0.85		2.54			
	0.85		2.58			
	0.80		2.52			
Ratio 4	0.80	0.82	2.6	2.71	1.36	31.18
	0.80		2.64			
	0.85		2.82			
	0.85		2.82			
	0.8		2.66			
Ratio 5	0.85	0.83	2.8	2.9	1.45	29.82
	0.80		2.88			
	0.80		2.98			
	0.85		3.0			
	0.85		2.82			

4.5.3: Formula 4 with API (Propranolol):

Table 4.23: Values of the excipients formulation with Propranolol for determining Carr's index and Hausner's ratio for formula 4

Ratio	Bulk volume V_o(ml)	Most acceptable volume of V_o (ml	Tapped volume Vr (ml)	Most acceptable volume of Vr (ml)	Housner ratio	Carr's index
Ratio 1	4.85	4.85	4.0	4.0	1.21	17.53
	4.8		4.1			
	4.8		4.1			
	4.85		4.0			
	4.8		4.1			
Ratio 2	4.7	4.7	4.1	4.0	1.18	14.89
	4.7		4.1			
	4.6		4.0			
	4.7		4.0			
	4.6		4.05			
Ratio 3	4.7	4.75	4.2	4.1	1.16	13.68
	4.7		4.2			
	4.75		4.1			
	4.75		4.1			
	4.75		4.1			
Ratio 4	4.7	4.8	4.2	4.2	1.14	12.5
	4.8		4.2			
	4.7		4.2			
	4.75		4.3			
	4.8		4.3			

Ratio 5	4.75	4.8	4.3	4.25	1.13	11.46
	4.8		4.25			
	4.7		4.25			
	4.8		4.3			
	4.7		4.3			

Table 4.24: Calculation of Angle of repose for formula 4 with propranolol

Ratio	Height (h)	Avg. Height (h)	Diameter (2r)	Avg. Diameter (2r)	Radius (r)	Angle of Repose
Ratio 1	0.9	0.9	2.5	2.53	1.27	35.23
	0.95		2.54			
	0.9		2.66			
	0.9		2.47			
	0.85		2.5			
Ratio 2	0.85	0.86	2.45	2.48	1.24	34.74
	0.85		2.46			
	0.9		2.5			
	0.9		2.58			
	0.8		2.4			
Ratio 3	0.8	0.83	2.5	2.55	1.28	32.96
	0.8		2.65			
	0.85		2.58			
	0.85		2.44			
	0.85		2.6			
Ratio 4	0.80	0.80	2.66	2.57	1.3	31.61
	0.80		2.62			
	0.80		2.52			
	0.80		2.55			
	0.80		2.5			
Ratio 5	0.80	0.79	2.7	2.65	1.33	30.71
	0.80		2.65			
	0.85		2.68			
	0.80		2.56			
	0.80		2.68			

4.5.4: Comparison between the ratios of three formulas in graph for F3

4.5.4.1: Hausner's ratio

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

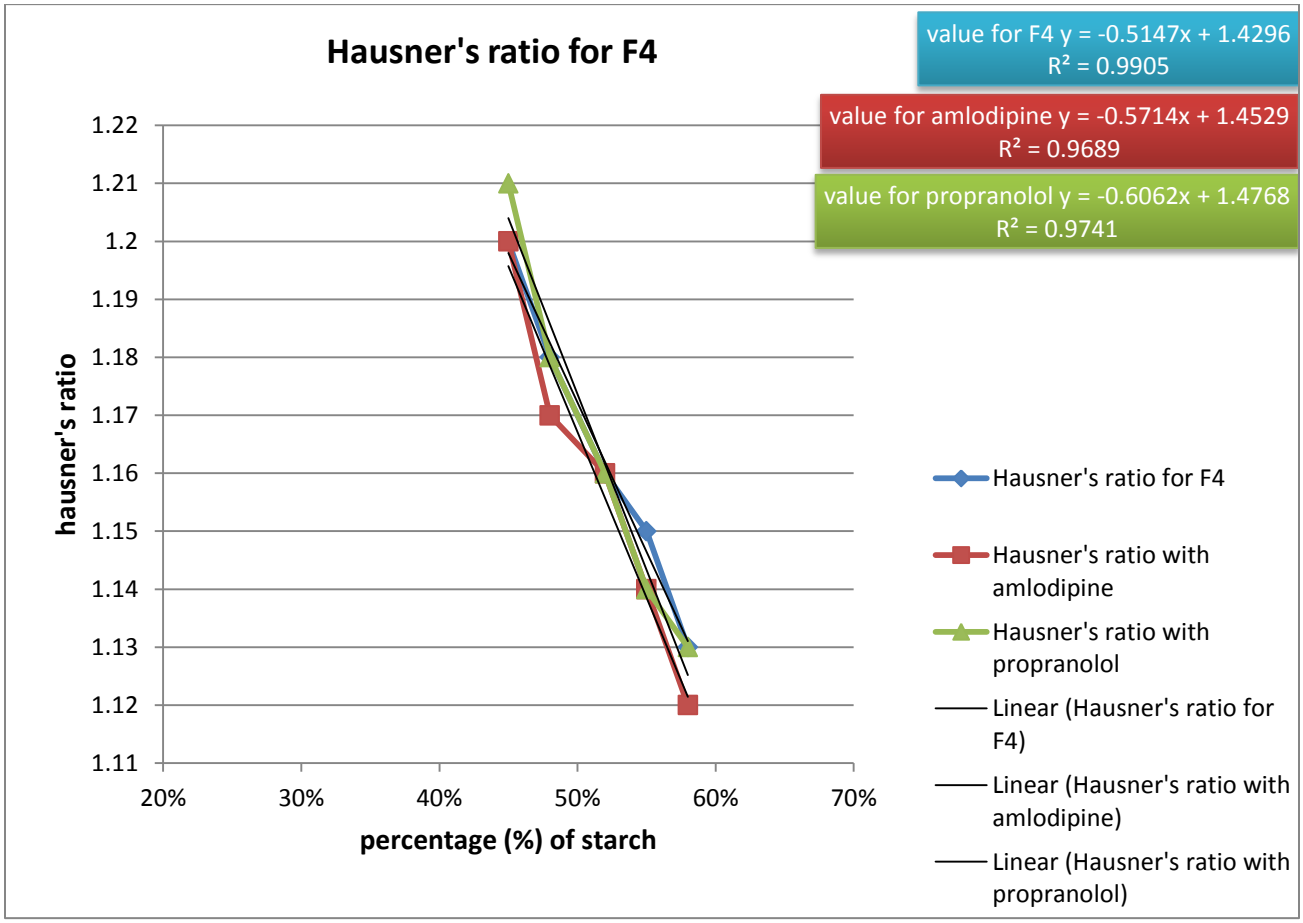

Figure 4.10: A percentage ratio of starch versus Hausner's ratio graph for F4

4.5.4.2: Carr's index

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

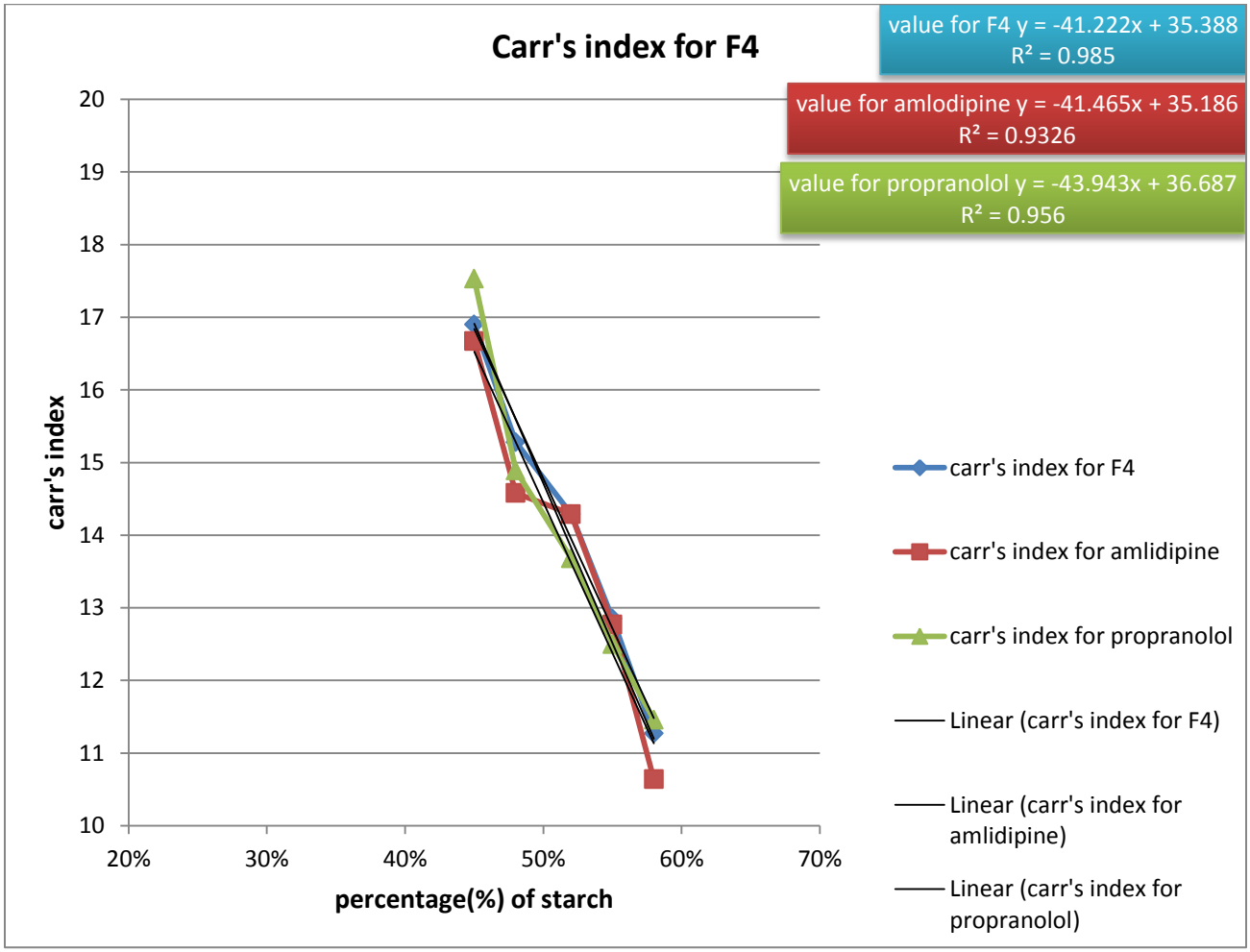

Figure 4.11: A percentage ratio of starch versus Carr's index graph for F4

4.5.4.3: Angle of repose:

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

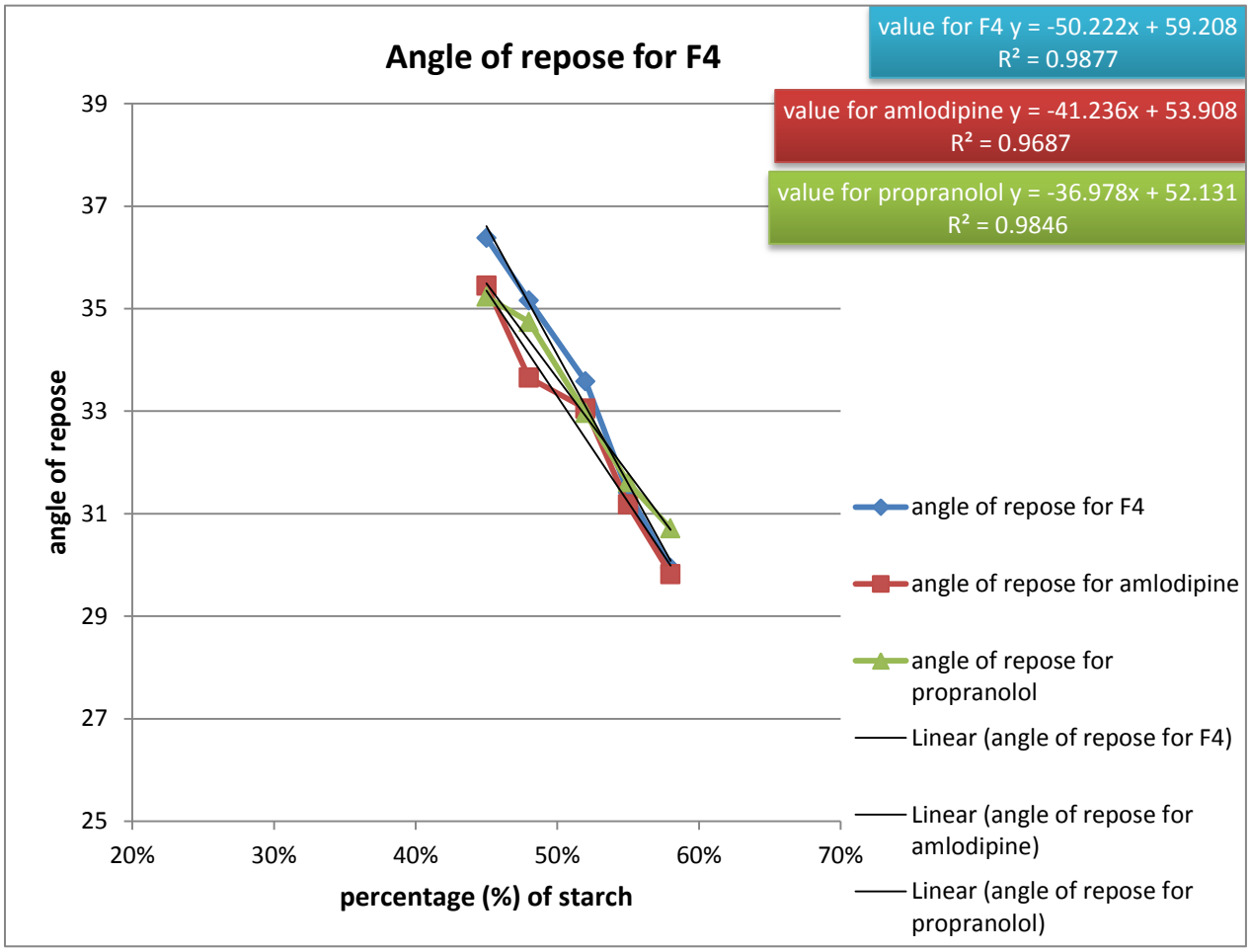

Figure 4.12: A percentage ratio of starch versus angle of repose graph F4

4.6 Equation and regression value of graph:

4.6.1: Equation and regression value for Hausner ratio:

Haunser ratio	Equation and regression value
F- 1	Y= -0.28x+ 1.526, R^2= 0.9245….(i)
F- 2	Y= -0.4388x+ 1.5135, R^2= 0.9599….(ii)
F- 3	Y= -0.08x+ 1.484, R^2= 0.973….(iii)
F- 4	Y= -0.5147x+1.4296 , R^2= 0.9905….(iv)
Value of amlodipine for F 1	Y= -0.42x+1.572 , R^2= 0.9423….(v)
Value of amlodipine for F 2	Y= -0.3626x+1.4689, R^2= 0.9855….(vi)
Value of amlodipine for F 3	Y= -0.7333x+1.454 , R^2= 0.9796….(vii)
Value of amlodipine for F 4	Y= -0.5714x+1.4529 , R^2= 0.9689….(viii)
Value of propanolol for F 1	Y= -0.38x+1.54 , R^2= 0.9025….(ix)
Value of propanolol for F 2	Y= -0.4132x+1.4978 , R^2= 0.9899….(x)
Value of propanolol for F 3	Y= -0.8x+1.486 , R^2= 0.9796….(xi)
Value of propanolol for F 4	Y= -0.6062x+1.4768 , R^2= 0.9741….(xii)

4.6.2: Equation and regression value for Carr's index:

Carr's index	Equation and regression value
F 1	Y= -13.24 x +34.59, R^2= 0.8431…. (i)
F 2	Y= -26.397x+ 35.765, R^2= 0.949…. (ii)
F 3	Y= -58.167x+ 37.084, R^2= 0.9775…. (iii)
F 4	Y= -41.222x+35.388 , R^2= 0.985….(iv)
Value of amlodipine for F 1	Y= -19.6x+36.378 , R^2= 0.8829….(v)
Value of amlodipine for F 2	Y= -25.612x+35.238 , R^2= 0.9829….(vi)
Value of amlodipine for F 3	Y= -51.167x+34.348 , R^2= 0.9797….(vii)
Value of amlodipine for F 4	Y= -41.465x+35.186 , R^2= 0.9326….(viii)

Value of propanolol for F 1	Y= -13.12x+32.872 , R^2= 0.9819….(ix)
Value of propanolol for F 2	Y= -23.219x+34.221 , R^2= 0.9475….(x)
Value of propanolol for F 3	Y= -60.26x+38.44 , R^2= 0.9355….(xi)
Value of propanolol for F 4	Y= -43.943x+36.687 , R^2= 0.956….(xii)

4.6.3: Equation and regression value for angle of repose:

Angle of repose	**Equation and regression value**
F 1	Y= -20.26x+52.762 , R^2= 0.9883….(i)
F 2	Y= -25.424x+50.078 , R^2= 0.9744….(ii)
F 3	Y= -48.667x+51.938 , R^2= 0.9894….(iii)
F 4	Y= -50.222x+59.208 , R^2= 0.9877….(iv)
Value of amlodipine for F 1	Y= -23.7x+53.316 , R^2= 0.9896….(v)
Value of amlodipine for F 2	Y= -22.277x+47.531 , R^2= 0.9905….(vi)
Value of amlodipine for F 3	Y= -57.933x+55.316 , R^2= 0.9493….(vii)
Value of amlodipine for F 4	Y= -41.236x+53.908 , R^2= 0.9687….(viii)
Value of propanolol for F 1	Y= -14.84x+49.584 , R^2= 0.8739….(ix)
Value of propanolol for F 2	Y= -25.788x+49.423 , R^2= 0.9686….(x)
Value of propanolol for F 3	Y= -44.467x+51.115 , R^2= 0.9845….(xi)
Value of propanolol for F 4	Y= -36.978x+52.131 , R^2= 0.9846….(xii)

Chapter five

Discussion

5.1 Discussion

This research paper is about to determine the flow propertied of different excipient combination with and without APIs with varying degree of diluent starch. The result of most of the combination was good but there were some with poor result because of combination and due to high percentage of binder. The result might vary because of human error as there was lack of expertise and also for environmental imbalance. I determined the flow property by hausner's ratio, carr's index and angle of repose. The values of Carr's index, Hausner's ratio and angle of repose were plotted against the percentage ratios of diluents. From these graphs the straight line equation for each set of formula were obtained which can be used to predict the flow property of these formula with different ratio of diluents and their compatibility with different types of APIs. In this research the straight line equation for APIs were compared with the excipient formula to identify the difference between the two results.

- In case of formula 1 the calculated value signified that the flow property increases with increasing degree of starch. From table 4.1 we can see that the value for Hausner's ratio and carr's index is decreasing with increasing amount of starch. Though the values of both hausner's ratio and carr's index were poor but they were improving with increasing amount of starch. The values of angle of repose form table 4.2 were also in passable range, only 60%:40% (Starch : Formula 1) ratio showed fair range of angle of repose and its value for hausner's ratio and carr's index were in passable range. The values with amlodipine and propranolol were same as the excipient formulation but they show differences than excipient. When compared in straight line equation (fig: 4.1) amlodipine showed better result than propranolol with formulation. Propranolol showed better result for hausner's ratio, carr's index and angle of repose with excipient. In case of formula 1 the results were not very satisfactory may be due to high percentage of binder used and for environmental imbalance.

  Flow property of different formulas can be easily understood from the table 4.6.1 for hausner's ratio. From these equations we can find out any desired flow property. For

example, if we consider equation (I) Y= -0.28x+ 1.526, R2= 0.9245; here Y value represents percentage of starch. For any percentage of starch the value for X can be determined with desired R value. Most desirable regression value determined for excipient formula for set-4 (equation IV: Y= -0.5147x+1.4296, R2= 0.9905) and for amlodipine and propranolol for set-2 (equation VI: Y= -22.277x+47.531, R2= 0.9905 and IX: Y= -13.12x+32.872, R2= 0.9819).

- In case of formula 2 (table 4.3), the most desirable result was observed for 65%:35% (Starch: Formula 2) ratio. For this ratio the range for hausner's ratio and carr's index was in fair range but angle of repose was changed to good range. Here the percentage for binder was same in formulation which might be a reason for poor result. As human error was less in this case formula 2. Here also the flow ability increases with increasing degree of diluent. The values of amlodipine and propranolol were similar to the excipient values. When the results were plotted into straight line equation all three formulation showed a good result. The result from the equation for both amlodipine and propranolol were increased than the excipient formulation equation.

- In case for formula 3, it showed better results than above two for hausner's ratio, carr's index and angle of repose (table 4.5 and 4.6). The reason behind this might be the ratio of the excipient used. Here percentage of binder was reduced than above two formulas. The best result was observed for 42%: 58% (Starch : Formula 3) ratio for all the flow ability criteria. In formula 3 the amount of starch was less, if they were used in higher amount the result might be improved from fair to good as flow properties are increased with increasing degree of starch. All the parameters were in good range for this ratio. When compared in straight line equation propranolol showed better value than amlodipine but both APIs flow property slightly improved from the excipient formulation.

- Formula 4 was found as the best among these four formulations as here a good percentage of starch was present and amount of binder was less. The observed values for

flow properties are shown in table 4.7 and 4.8. The flow ability is increasing with increasing amount of starch. Best result found for the ratio 58%: 42% (Starch : Formula 4). The result for this ratio was in excellent range for hausner's ratio, carr's index and also for the angle of repose. After plotting the values in graph and formed a straight line equation, three values for excipient, amlodipine and propranolol were compared. Propranolol showed best compatibility with these ratios than amlodipine. For this reason the result for amlodipine was less than propranolol. Also the values for hausner's ratio, carr's index and angle of repose for propranolol was moro similar to excipient formula than amlodipine.

Chapter six

Conclusion

6.1 Conclusion

Flow property of pharmaceutical solid dosage forms has particular interest from the pharmaceutical industries. Improved or faster flowability will increase the production of solid dosage forms. As diluents are used as a major portion of a solid dosage form, its flow property is of particular interest are increased. This experiment was done to determine several equations of formulation with several ratios of diluents. As we also have shown the flow properties of different formulation with APIs and their differences it will help the other people working with these type of formulation for solid dosage form. It will also help them by saving money and time by following the graph and their differences.

Chapter seven

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