Determination of variation in Flow Property of Different Formulas of PEG (Polyethylene Glycol) along with Amlodipine and Propranolol

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

In the name of aLLah

The mosT Gracious and mosT merciful

DEDICATION

This Research Project Is Dedicated to My Beloved Parents.

DECLARATION BY THE CANDIDATE

I, Sanjida Rahaman Shanta, hereby declare that the dissertation entitled "**Determination of variation in Flow Property of Different Formulas of PEG (Polyethylene Glycol) along with Amlodipine and Propranolol**", submitted by me to the Department of Pharmacy, East West University, in the partial fulfillment of the requirement for the degree of Bachelor of Pharmacy with original research work carried out by me under the supervision and guidance of Mohammed Faisal Bin Karim, Senior Lecturer and Under co-Supervision of 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 PEG (Polyethylene Glycol) along with Amlodipine and Propranolol**", submitted to the Department of Pharmacy, East West University, in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy was carried out by Sanjida Rahaman Shanta (ID: 2011-3-70-020) under our guidance and supervision and that no part of the research has been submitted for any other degree. We further certify that all the sources of information and laboratory facilities availed of in this connection is duly acknowledged.

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CERTIFICATE BY THE CHAIRPERSON

This is to certify that the dissertation entitled "**Determination of variation in Flow Property of Different Formulas of PEG (Polyethylene Glycol) along with Amlodipine and Propranolol**", is a genuine research work done by Sanjida Rahaman Shanta (ID: 2011-3-70-020) under the guidance and supervision of Mohammed Faisal Bin Karim, Senior Lecturer, and Md. Anisur Rahman (co-supervisor), Senior Lecturer, Department of Pharmacy, East West University, Dhaka.

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Abstract

The objective of this research project was to evaluate the flow property of different sets of Formulas of Amlodipine and Propranolol along with PEG (Polyethylene Glycol) individually and in combination as well. Here we tried to focusing to isolate a specific equation which explain the flowability of a formulation.we had measured several parameters, such as, bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose for different mixture of same pharmaceutical recipients but in different ratio. For accurate result the experiments were done four times and all the guidelines were followed. By evaluating the laboratory experimental data, we were able to determine several specific equations (y= mx + c) for particular mixtures of specific pharmaceutical excipients. My work was based on the variation in flowability of mixtures due to the presence of different amount of binders. Flow property of pharmaceutical excipients for a new drug formulations can be predicted and measured by these equations

Keywords: Binder, Flowability, Bulk density, Tapped density, Carr's index, Hausner ratio and Angle of Repose

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CHAPTER ONE

Introduction

1.1 Introduction

Our objective is to evaluate that ratio of pharmaceutical excipients in a mixture that will provide maximum flow property. Flow property means the physical properties of moving ability of pharmaceutical powders. It is very much important in the pharmaceutical industry for the operations such as blending, tablet compression, capsule filling, transportation, and in scale-up operation. 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 property

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 nonflowing. (Drugs.com, 2015)

The flow property of powder plays an important role in dosage form manufacturing process. When limited amounts of drugs are available these can be evaluated simply by measurement of bulk density and angle of repose. Powder flow is a key requirement for pharmaceutical manufacturing process. Tablets are often manufactured on a rotary multi-station tablet press by filling the tablet die with powders or granules based on volume. Thus, the flow of powder from the hopper into the dies often determines weight, hardness, and content uniformity of tablets. In case of capsules manufacturing, similar volume filling of powders or granules is widely used. Understanding of powder flow is also crucial during mixing, packaging, and transportation. And thus, it becomes essential to measure the flow properties of these materials prior to tableting or capsule filling (Freemantech, 2013)

1.2.1 Factors influencing the flow property of powders:

1. Particle size
2. Particle shape
3. Porosity
4. Density of bulk powder
5. Moisture content

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

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

3. **Moisture**: The effect of moisture on flowability of particles varies from powder to powder. The particles become cohesive due to moisture absorption. In presence of excessive moisture, the powder shows poor flowability. In this experiment, I have used desiccant in different powder bulk to remove the moisture content from the powder and maximize the flow characteristic of the powders used
4. **Electrostatic effects**: The charged material show poorer flow than uncharged material. Particles can acquire static charges by grinding, collision, mixing, sieving and moisture. In this experiment, this factor is maintained properly.

5. **Powder cohesion and storage compaction**: When solid remains at rest or stored in a hopper or bin, it can become more cohesive and gives poor flow.
6. **Effect of temperature**: Temperature is a very influential factor for flow property. Higher or lower the temperature can make the powder degrade and also hamper natural flow behavior. So in this experiment the temperature of the laboratory was maintained at room temperature at which the powders generate its natural quality.

1.2.2 Flow properties can be improved by-

- ❖ Powder processes into granules of spherical shape
- ❖ Choosing optimal size of granules (400 to 800 um)
- ❖ Incorporating optimum amount of fines (about 15% w/w)
- ❖ Incorporating optimum concentration of lubricants (Magnesium stearate, Talc etc.)

1.2.3 Parameters of measuring flow properties of powders

The physical properties of pharmaceutical powders are of upmost importance in the pharmaceutical industry. 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,

For free flowing particles-

- ✓ Angle of repose,
- ✓ Compressibility index or Hausner ratio and
- ✓ Flow rate through an orifice,

For cohesive particles-

- ✓ Shear cell

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

1.2.3.1 Angle of Repose

Angle of repose is used to measure frictional forces in a loose powder. The angle that the plane of contact between two bodies makes with the horizontal when the upper body is just on the point of sliding is called the angle of repose. The angle of repose is the angle which is relative to the horizontal base of the conical pile produced when a granular material is poured on to a horizontal surface. It is also known as the critical angle of repose. The angle of repose can range from 0° to 90°. Lower the angle of repose, better the flow property (Merriam, 2013)

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

Figure 1.1: Angle of Repose

Table 1.1: Relation between angle of repose and type of flow & type of powder

Angle of Repose	Type of Flow	Type of Powder
<25	Excellent	Non cohesive
25-30	Good	Non cohesive
30-40	Passable	Cohesive
>40	Very poor	Very Cohesive

The tangent of angle of repose is equal to the coefficient of friction, μ, between the particles.

$$\mathbf{Tan\ \theta = \mu}$$

Hence the rougher and more irregular the surface of the particle the higher the angle of repose. Angle of repose can be calculated by

$$\mathbf{\theta = tan\ -1(h/r)}$$

Where h= height of the pile

r = radius of the base of the pile

θ = angle of repose

1.2.3.2 Methods in determining the angle of repose:

Tilting box method

This method is appropriate for fine-grained, non-cohesive materials, with individual particle size less than 10 mm. The material is placed within a box with a transparent side to observe the granular test material. It should initially be level and parallel to the base of the box. The box is slowly tilted at a rate of approximately 0.3 degrees/second. Tilting is stopped when the material begins to slide in bulk, and the angle of the tilt is measured.

Fixed funnel method

The material is poured through a funnel to form a cone. The tip of the funnel should be held close to the growing cone and slowly raised as the pile grows, to minimize the impact of falling particles. Stop pouring the material when the pile reaches a predetermined height or the base a predetermined width. Rather than attempt to measure the angle of the resulting cone directly, divide the height by half the width of the base of the cone. The inverse tangent of this ratio is the angle of repose.

Revolving cylinder method

The material is placed within a cylinder with at least one transparent face. The cylinder is rotated at a fixed speed and the observer watches the material moving within the rotating cylinder. The effect is similar to watching clothes tumble over one another in a slowly rotating clothes dryer. The granular material will assume a certain angle as it flows within the rotating cylinder. This method is recommended for obtaining the dynamic angle of repose, and may vary from the static angle of repose measured by other methods. When describing the angle of repose for a substance, always specify the method used. (US Pharmacopoeia 29-NF24)

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

1.2.3.3 Factors that influence the angle of repose:

- Decrease in particle size leads to higher angle of repose
- Lubricants at low concentration decrease the angle of repose and at high concentration enhance the angle of repose.
- Fines (pass through 100 meshes) increase the angle of repose.
- Rough and irregular surface, higher angle of repose(Authorstream, 2013)

1.2.3.4 Compressibility index and Hausner ratio

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

1.2.3.4.1 Compressibility index:

It relates with flow rate, cohesiveness and particle size. The Carr's index also known as

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

$$Compressibility\ Index = 100 \times \left(\frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}} \right)$$

$$Hausner\ \ Ratio = \left(\frac{\rho_{tapped}}{\rho_{bulk}} \right)$$

The Carr's index is frequently used in pharmaceutics as an indication of the flowability of a powder. In a free-flowing powder, the bulk density and tapped density would be close in value; therefore, the Carr's index would be small. On the other hand, in a poor-flowing powder where there are greater interparticle interactions, the difference between the bulk and tapped density observed would be greater, therefore, the Carr's index would be bigger. (Friedman and Robinson, 2002).

Table 1.2: Relationship between % compressibility index and powder flow ability.

S. No.	% compressibility index	Type of Flow
1.	5-12	Excellent
2.	12-16	Good
3.	18-21	Fair to Passable
4.	23-35	Poor
5.	33-38	Very Poor
6.	< 40	Very Very Poor

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

1.2.3.4.2 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 (1900–1995). The Hausner ratio is used in a wide variety of industries as an indication of the flowability of a powder. A Hausner ratio greater than 1.25 is considered to be an indication of poor flowability and less than 1.25 is considered to be an indication of free flowing.

The compressibility index and Hausner ratio are not intrinsic properties of the powder. They depend on the methodology used. (Malave et al., 1985; Barbosa and Yan, 2003)

Table 1.3: Relation between flow properties with Compressibility index (Carr's index) and Hausner ratio

Compressibility index (per cent)	Flow Character	Hausner Ratio
1-10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
> 38	Very, very poor	> 1.60

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

1.2.4 Bulk density and Tapped density

1.2.4.1 Bulk density:

Bulk density is defined as the mass of powder divided by its bulk volume. The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the interparticulate void volume. The bulk density depends on both the density of powder particles and the spatial arrangement of particles in the powder bed. It is expressed in grams per ml (g/ml) or grams per cubic centimeter and the international unit is kilograms per cubic meter as the bulk density is measured in cylinders. It may also be expressed in grams per cubic centi meter (g/cm3)

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

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. (Pharmacopeia, 2013)

1.2.4.2 Tapped density*:*

The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. It is the maximum packing density of a powder (or blend of powders) achieved under the influence of well-defined, externally applied forces.

The tapped density is obtained by mechanically tapping a graduated 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 mechanical tapping is achieved by raising the cylinder or vessel and allowing it to drop, under its own mass, a specified distance by either of three methods as described below. Devices that rotate the cylinder or vessel during tapping may be preferred to minimize any possible separation of the mass during tapping down. (Pharmacopeia, 2013).

The minimum packed volume thus achieved depends on a number of factors including particle size distribution, true density, particle shape and cohesiveness due to surface forces including moisture. Therefore, the tap density of a material can be used to predict both its flow properties and its compressibility (Wikianswers, 2013).

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

• Bulk volume = volume of powder + volume of intra particle space + voids

• True volume = the volume of powder itself

• Bulk density = mass/untapped volume

• Tapped density = mass/tapped volume (Slideshare, 2012).

1.3 Pharmaceutical excipients

Excipients are components of a finished drug product other than the active Pharmaceutical ingredient (API) and are added during formulation for a specific purpose. Although listed as inactive ingredients by FDA, excipients generally have well-defined functions in a drug product. As with active ingredients, they may be Small Molecule or complex and may vary in terms of degree of characterization. They may be chemically synthesized or may be either natural source or biotechnology-derived (recombinant). In Contrast to active ingredients, minor components of an excipient may have significant impact on its pharmaceutical performance. Depending on the intended use, an excipient in a drug product may be an active ingredient in another drug product.

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

1.3.1 Functions of excipients: (Drug.com, 2015)

Excipients are used in tablet formulation to perform a variety of functions like-

- ✓ Reducing the adhesion between the powder (granules) and the punch faces and thus prevent sticking to tablet punches by offering a non-stick surface. They are also used to help protect tablets from sticking. (antiadherants)
- ✓ Holding 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.(binders)
- ✓ Disintegrants expand and dissolve when wet causing the tablet to break apart in the digestive tract, releasing the active ingredients for absorption. They ensure that when the tablet is in contact with water, it rapidly breaks down into smaller fragments, facilitating dissolution
- ✓ Glidants are used to promote powder flow by reducing interparticle friction and cohesion. These are used in combination with lubricants as they have no ability to reduce die wall friction.

- ✓ Lubricants prevent ingredients from clumping together and from sticking to the tablet punches or capsule filling machine. Lubricants also ensure that tablet formation and ejection can occur with low friction between the solid and die wall
- ✓ Colors are added to improve the appearance of a formulation and to identify the product . these enhance patient acceptance
- ✓ For enhancing stability (antioxidants, uv absorbers) (USP29-NF24, 2013).

1.3.2 List of pharmaceutical excipients of various classes

Most commonly used excipients in pharmaceutical preparations are usually:

- ➢ Fillers.
- ➢ Binders.
- ➢ Disintegrants.
- ➢ Coatings.
- ➢ Sorbents
- ➢ Antiadherent.
- ➢ Lubricants.
- ➢ Glidants.
- ➢ Preservatives.
- ➢ Antioxidants.
- ➢ Flavoring Agents.
- ➢ Sweetening Agents.
- ➢ Coloring Agent (Haywood and Glass, 2011)

1.3.2.1 Fillers/Diluents: A diluent (also referred to as filler, dilutant or thinner) is a diluting agent. They typically also fill out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use.

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

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

- ✓ to enhance bulkiness
- ✓ to provide improved cohesion
- ✓ to enhance flow
- ✓ to allow direct compression manufacturing

1.3.2.1.2 Selection of diluents: To select a diluents/Filler we must consider the following factors-

- ✓ Compatibility
- ✓ Flowability
- ✓ Solubility
- ✓ disintegration qualities
- ✓ hygroscopicity
- ✓ lubricity
- ✓ stability

1.3.2.1.3 Function of fillers: Fillers add volume and/or mass to a drug substance, thereby-

- ✓ facilitating precise metering and handling thereof in the preparation of dosage forms used in tablets and capsules

1.3.2.1.4 Typical features of fillers: Diluents/filler for tablet must meet some criteria. They are as follows-

- ➢ Diluents must be inert
- ➢ They must be nontoxic
- ➢ They must be biocompatible
- ➢ They must be acceptable
- ➢ They must have consistent physical and chemical characteristics
- ➢ Diluents must be non-hygroscopic
- ➢ They must be non-conducive to microbiological
- ➢ They must be commercially available in acceptable grades
- ➢ They must be color-compatible
- ➢ They must have no deleterious effect on bioavailability of drugs.
- ➢ Diluents should preferably be colorless or nearly so. (Patel, Shah and Upadhyay, 2015)

1.3.2.2 Binder:

Binder is one of an important excipient to be added in tablet formulation. In simpler words, binders or adhesives are the substances that promote cohesiveness. It is utilized for converting powder into granules through a process known as Granulation. Granulation is the unit operation by which small powdery particles are agglomerated into larger entities called granules.

1.3.2.2.1 Commonly used Binders

- **Sugars :**
  - ✓ Sucrose
  - ✓ Liquid glucose
- Natural Binders:
  - ✓ Acacia
  - ✓ Tragacanth
  - ✓ Gelatin
  - ✓ Cellulose
- Synthetic/Semisynthetic polymers:
  - ✓ Methyl cellulose
  - ✓ Ethyl cellulose
  - ✓ Hydroxy propyl methyl cellulose
  - ✓ Hydroxy propyl cellulose
  - ✓ Polyvinyl Pyrrolidone (PVP)
  - ✓ Polyvinyl Glycol (PEG)

1.3.2.2.2 Evaluation tests for Binders/Granules

Compactness, physical and chemical stability, rapid production capability, efficacy are some of the characteristics that make tablet a ruling dosage form. These characteristics depend on the quality of granules from which it is made. The characteristics of granules produced are affected by formulation and process variables. So it becomes essential to evaluate the granule characteristics to monitor its suitability for tableting. (Mattsson, 2013)

1.3.2.3 Disintegrant:

Disintegrating agents is a substance or mixture of substances added to tablets to facilitate its break up or disintegration. The active constituents must be released from the tablet as efficiently as possibleto allow its rapid action. Hence the therapeutic action is based on the amount of drug released from the tablet, these disintegrants which allows rapid de-aggregation of solid in to solution and followed by which absorption of the drug takes place. Most of the conventional and in novel preparation the impact of distegrants had given a new dosage form such as rapid disintegrating tablets and mouth dissolving tablets. By fair choice of the disintegrating agents which has a greater impact in the final formulation to enhance the drug bioavailability. (Gohel, 2015)

1.3.2.3.1 Ideal characteristics of disintegrants:

- Poor solubility
- Poor gel formation
- Good hydration capacity
- Good molding and flow properties
- No tendency to form complexes with the drugs

1.3.2.3.2 Factors affecting action of disintegrants

- Percentage of disintegrants present in the tablets.
- Types of substances present in the tablets.
- Combination of disintegrants.
- Presence of surfactants.
- Hardness of the tablets.
- Nature of Drug substances.
- Mixing and Screening.

1.3.2.3.3 Commonly used Disintegrants used in tablets:

- ✓ Starch
- ✓ Polyvinylpyrrolidone (PVP),
- ✓ sodium carboxymethyl cellulose,
- ✓ Sodium Starch Glycolate
- ✓ Microcrystalline cellulose (Pformulate, 2000).

1.3.3 Lubricants:

Lubricants are the 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 by boundary mechanism, results from the adherence of the polar portions of molecules with long carbon chains to the metal surfaces to the die wall. Magnesium stearate is an example of boundary lubricant. Other is hydrodynamic mechanism i.e. fluid lubrication where two moving surfaces are separated by a finite and continuous layer of fluid lubricant. Since adherence of solid lubricants to the die wall is more than that of fluid lubricants, solid lubricants are more effective and more frequently used.

Lack of adequate lubrication produces binding which can results in tablet machine strain and can lead to damage of lower punch heads, lower cam track, die seats and the tooling itself. And it may also yield tablets with scratched edges and are often fractured at the top edges. With excessive binding the tablet may be cracked and fragmented by ejection.

1.3.3.1 Functions of Lubricants:

There are three roles identified with lubricants as follows:

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

1.3.3.2 Ideal characteristics of Lubricants:

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

1.3.3.3 Classification of lubricants

Lubricant are classified according to their water solubility i.e. water insoluble and water soluble. Selection of lubricant is depends partly on mode of administration, type of tablet, desired disintegration and dissolution properties, physicochemical properties of granules or powder and cost.

1.3.3.4 Commonly used Lubricants in tablets

Insoluble Lubricants

- ✓ Magnesium Stearate,
- ✓ Calcium Stearate,
- ✓ Sodium stearate
- ✓ Talc

Water soluble Lubricants

- ✓ Boric acid
- ✓ Sodium Lauryl sulfate (SLS)
- ✓ Magnesium Lauryl sulfate (MLS)
- ✓ Sodium benzoate

1.3.4 Antiadherents:

Antiadherents are used to reduce the adhesion between the powder (granules) and the punch faces and thus prevent sticking to tablet punches. They are also used to help protect tablets from sticking.

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

1.3.4.1 Commonly used Antiadherents:

- Talc (1 – 5%),
- stearates like Mg stearate,
- Zn stearate and corn starch (3 – 10%),
- Sodium lauryl sulfate (less than 1%)

1.3.5 Glidants

Glidants are added to the formulation to improve the flow properties of the material which is to be fed into the die cavity and aid in particle rearrangement within the die during the early stages of compression. If the flow properties are extremely poor then glidants are ineffective and consideration of force free mechanisms may be necessary.

1.3.5.1 Commonly used Glidants

- Starch is a popular glidant because it has additional value of disintegrant. Concentration of starch is common up to 10%, but should be limited otherwise it will worsen the flow of material.
- Talc is a glidant which is superior to starch; its concentration should be limited because it has retardant effect on dissolution-disintegration profile.
- Silaceous material like colloidal silica i.e. syloid, pyrogenic silica (0.25%), hydrated sodium silioaluminate (0.75%) are also successfully used to induce flow.

Glidants act by interposing their particles between those of material and lower the overall interparticulate friction of the system by virtue of their reduced adhesive tendencies. Similar to lubricants, they are required at the surface of feed particles and they should be in fine state of division and appropriately incorporated in the mixture.

1.4 Excipients used in the experiment

- Starch
- Magnesium Stearate
- Zinc stearate
- Talc
- Calcium phosphates
- Carboxy methyl cellulose (CMC)
- Lactose
- Polyethylene glycol (PEG)
- Polyvinyl Pyrrolidone (PVP)

1.4.1 Starch Starch was used as diluent or filler. It is a white powder without any odor or taste. Native starches are available from a wide variety of plant sources such as corn, potato and wheat. However, these varieties tend to be highly viscous, to agglomerate, and have poor flow properties, making their handling difficult during the tablet manufacturing process**.** They make the required bulk of the tablet when the drug dosage itself is inadequate to produce tablets of adequate weight and size

1.4.2 Magnesium Stearate Magnesium stearate is the most commonly used and most effective of all lubricants and as well as antiadherant. It is also the most likely to cause compression & dissolution problems. Concentration, grade and mixing parameters must be carefully controlled. These stearates are alkaline in reaction. It is incompatible with strong acids, alkalis, and iron salts.

1.4.3 Zinc stearate It is very common pharmaceutical recipients which is used as antiadherant as well as lubricant.It is added to reduce sticking or adhesion of any of the tablet granulation or powder to the faces of the punches or to the die wall. It is intended to reduce the friction during tablet formation in a die and also during ejection from die cavity.

1.4.4 Calcium phosphates We used it as diluents. Bulk density of calcium phosphates is higher than that of organic fillers. They are directly compressible and are characterized by brittle fracture on compression during tableting process. Hard tablets are produced when calcium phosphates are used as diluents. They exhibit good flow properties

1.4.5 Lactose Lactose is widely used as diluents. Several grades are available such as Lactose monohydrate, spray dried lactose and anhydrous lactose. It has no reaction with most active ingredients. Lactose on storage tends to lose moisture.

1.4.6 Polyethylene glycol (PEG) PEG 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. It is added to tablet formulation to add cohesiveness to powders, thus providing necessary bonding to form granules, which under compaction form a cohesive mass or a compact. (Dow, 2011).

1.4.7 Polyvinyl pyrrolodone (PVP) PVP acts as binder as well as lubricant due to its structure and physical properties. It is commonly used recipients in pharmaceutical industries. It is a polymer available in different grades depending on the molecular weight. It is soluble in water and other solvents generally used in pharmaceutical manufacturing. It acts as a binding agent for wet granulation and direct compression methods. Some grades of povidone are also useful in the preparation of sustained release tablets.

1.4.8 Talc It is 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).Talc incompatible with quaternary ammonium compounds. It is not soluble in water**. (**Rowe, Sheskey and Quinn, 2009)

Chapter two

Literature review

Determination of variation in Flow Property of Different Formulas of PEG (Polyethylene Glycol) along with Amlodipine and Propranolol

In the year 1965, Gold and Palermo (Gold and Palermo, 1965) did an experiment to determine the antistatic properties of tablet lubricants such as magnesium stearate, polyethylene glycol 4000, sodium lauryl sulfate and talc. They found that these lubricants have the ability to lower the accumulation of static charges which results the flow of material through a tablet hopper. Their result showed that different highly static materials influence the antistatic properties of these lubricants. The concentration of lubricant gets lower, when the antistatic effectiveness is decreased.

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

After three years later in 1982, two scientists, Mckenna and Mccafferty (Mckenna and Mccaferty, 1982) did an experiment to show the effect of particle size on the compression mechanism and tensile strength of prepared tablets. In the experiment they found that declining the particle size of spray-dried lactose and Sta-Rx 1500 resulted in stronger compaction. On the other hand, particle size variation of Avicel PH-101 did not showed any impact on tablet tensile strength. Their result of study identified 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.

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

In 1990, two scientists Tan and Newton (Tan and Newton, 1990) evaluated the flowability of pharmaceutical excipients related to their capsule filling performance. 20 capsules were used as an indicator of capsule filling performance. As flowability was dependent on the particle size, morphology and bulk density of the powder there was a significant correlation between the values of *X*cv and the flow parameters of Carr's compressibility, Hausner's ratio, angle of repose, Kawakita's equation constant (*a*) and Jenike's flow factor. *X*cv was also related to the coefficient of variation of the powder bed bulk density and the variation in the compression stress.

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

In the same year 1994, the two scientists 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 purpose of 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. 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.

After one year, two scientists, Flemming and Mielck (Flemming and Mielck, 1995) studied the effect of eleven pharmaceutical excipients with Avicel PHI02 SCG. 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.

The same year, Eino Nelson (Nelson, 1995) studied the problems of granulation flow in tablet manufacturing. He studied the angle of repose of sulfathiazole where he found that the AOR increased with decrease of particle size. Addition of talc to the granules in small portion decreased the repose angle. He also found that Magnesium stearate caused little or no effect on the repose angle of the granulation. However, addition of fines to coarse granules had a striking increase in AOR.

The next year, a comparative investigation was performed by Talukdar and other scientists (Talukdar et al., 1996) between xanthan gum and HPMC which act as hydrophilic matrix-forming agents. The objective was to observe the compaction characteristics and drug release behavior of these materials. Though the compaction characteristics were found similar but the flow characteristics were different. He found that HPMC was less flowable than xanthan gum which significantly affected 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.Fumed silicon dioxide, magnesium stearate, starch, and talc in combination with a set of selective materials were used. 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.

The same year, also two scientists Rajesh Patel and Fridrun Podczeck (Patel and Podczeck, 1996) investigated 8 microcrystalline cellulose samples on the capsule filling performance. Different sources of fine, medium and coarse grade microcrystalline cellulose were used. They determined the Kawakita constant and Hausner's ratio as the indicators of the capsule filling performance. A fine grade microcrystalline cellulose such as Avicel® PH105 cannot be used in capsule filling because of unsatisfactory flow properties.

After three years back, Feeley and his co workers (Feeley et al., 1998) did experiment to evaluate 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). To check out the relationship between powder flow and the surface energetic properties a powder flow analyzer was used . The potential of these techniques to identify and measure differences in powder samples, before and after micronisation was found.

The next year, two scientists E.C. Abdullah and D. Geldart (Abdullah and Geldart, 1999) measured the bulk density of powders with two equipments (the Hosokawa Powder Tester and the Copley Tap Density Volumeter) to evaluate the flow property of porous and nonporous powders. 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 accurate 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 afterward 2000, Taylor and Ginsburg (Taylor and Ginsburg, 2000) tested the flow properties of typical tablet and capsule formulation excipients, active ingredients and the representative formulation for identifying a definite and precise testing operation for powder flow measurement. Here the test parameters were angle of repose, compressibility index and critical orifice. After establishment of the empirical composite index, powder flow had been determined with respect to principal component, analysis of angle of repose and critical orifice of the powder

material. The research proved that improvements of test instruments and further studies are necessary for better assessment of these approaches.

In the Same year, three scientists 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.

The next year, a Chinese scientist, Anthony Chi-Ying Wong (Wong et al., 2002) did an experiment on the angle 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 measurements.

In 2003, Mullarney and his research team (Mullarney et al., 2003) studied on the physical flow and mechanical properties of common pharmaceutical excipients (sweeteners) that are frequently used in solid dosage form formulation. Here stated that the selected sweeteners have different particle size, shape and true density. Their powder flow characteristics, mechanical properties and cohesivity test were performed. They found that some sweeteners such as sucrose and acesulfame potassium showed excellent flowability whereas saccharin sodium and aspartame were proven poor flowable substances. So, it can be stated that, a careful selection of suitable sweetener is mandatory to obtain desirable flowability.

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

In the same year, 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. They found that 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.

The next year in 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 result was compared with the value of the flowability measurements. The correlated rank order of the formulations was considered the same with all the techniques. The measured flow properties directly reflect the behavior of the tablet formulation during powder mixture procedure.

The same year, Thalberg, Lindholm and Axelsson, (Thalberg et al., 2004) investigated the comparison of different flowability tests for powders for inhalation. A series of placebo powders for inhalation was examined. A modified Hausner Ratio, the Aero Flow, Uniaxial tester and the angle of repose was measured. The modified Hausner Ratio discriminated well between the investigated powders and seemed 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.

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

In the next year, Bagster and Crooks (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 2008, Hou and Sun (Hou and Sun, 2008) did an experiment to determine 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 the same year, Rakhi Shah (Shah, 2008) 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.

In 2009, Erica Emerya (Emerya, 2009) investigated the effect of moisture content on four pharmaceutical powders (an active pharmaceutical ingredient (API), Aspartame, Hydroxypropyl Methylcellulose (HPMC), and Respitose). The Aspartame was tested at moisture contents of 0%, 2%, 5%, and 8% and the HPMC was also tested at moisture contents of 0%, 2%, 5%, and 10%. Powder flowability was measured using the Jenike shear index, the Hausner Ratio, the Carr Index, and the static and dynamic angles of repose. The flowability of Aspartame increased with an increase in moisture content.The flowability of HPMC decreased with an increase in moisture content due to the increasing strength of liquid bridges.

In the same year 2009, Meer Saiful Hassan and Raymond Wai Man Lau (Hassan and Raymond, 2009) compared the flowability with similar size range particles of different shapes such as sphere, needle, cube, plate and pollen. Flowability of the particles was characterized by Carr's compressibility index and angle of slide (θ) method. Pollen-shaped particles are found to exhibit better flowability than particles of other shapes in similar size range. They showed minimum θ of 35°. They suggested that the use of pollen-shaped particles can be a potential improvement in dry particle inhalation .

The next year 2010, Gerald Gold (Gold, 2010) 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.

The same year, Sun (Sun, 2010) did an experiment and discovered that in tablet manufacturing process an inadequate powder flow leads to a great problem. Besides, a minimum knowledge of flow properties for efficient pharmaceutical tablet development is required for successful tableting result.This data also can serve as a reference value for comparing with other prototype formulation. The research concluded that a poor flowing powder exhibit flow problems should be avoided and further implementation of this approach can minimize the problem associated with flow measurement during large scale production.

In the same year 2010, Sarraguca and his co-workers (Sarraguca et al., 2010) determined the flow properties of pharmaceutical powders by near infrared spectroscopy. They illustrated that physical properties of pharmaceutical powders are of topmost importance in the pharmaceutical industry. They examined the critical significance of flow properties on processes like blending, tablet compression, capsule filling and transportation using angle of repose, Carr's's index and Hausner ratio. They used near infrared spectroscopy which is a fast and low-cost analytical technique to determine the parameters of flow properties of pharmaceutical powders based on

active ingredient paracetamol. The spectra were recorded on a Fourier-transform near infrared spectrometer in which the parameters were the angle of repose, true and tapped density. The comparison was made between near infrared based properties and reference methods results. The result showed that the physical properties affect the flowability of pharmaceutical powders.

In 2011, Chattoraj, Shi and Sun (Chattoraj, Shi and Sun, 2011) discovered that poor flow properties hinder the easy handling of powders during industrial-scale processing. In their experiment, they also showed that powder flow can be considerably improved by reducing the cohesion of powders by coating them with nanosized guest particles. Optimum flow enhancement has been made with specified preparation at vigorous mixtures. The flow properties of nanocoated Avicel PH105 are comparable to those of Avicel PH102, which exhibits adequate flowability for processing on a high-speed tablet press. The result showed that the technique proved as a potential source for addressing industrial powder handling problems caused by poor powder flow properties.

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 critical moisture content and for corn starch, it was increased. Flowability of HPMC was not changed that much. The dynamic density of the celluloses and PVP decreased linearly with increasing moisture content as the particles swelled with water.

In the same year 2013, Morin and Briens (Morin and Briens, 2013) 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 the same year, an experiment was done by two scientists Garett and Lauren (Garett and Lauren, 2013).They 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.

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, Traina and other five researchers from Belgium (Trainaa et al., 2013) carried out measurements of compressibility on five granular materials; those are two different lactose powders, hydrated lime Ca(OH)2, yttrium stabilized zirconia balls and polystyrene balls. Here, additional air volume was added to the optimal granular packing. The found that if the powder is cohesive, it traps more air compared with the non-cohesive or free flowing powder which traps very small amount of air in static state and this free flowing powder improves the speed of packaging.

Most recently, in 2015 an experiment was done by Woo, Lugito, and Tsai (Woo, Lugito, and Tsai, 2015).They observed the effects of top confinement and diluent polyethylene oxide (PEO) on poly(l-lactic acid) (PLLA) crystal morphology. They found uncovered neat PLLA sample exhibits higher growth rate ringlessspherulites when crystallized at 120°C; while the covered sample exhibits lower growth rate ring-banded spherulites. As PEO is introduced into PLLA, the morphology also undergoes significant changes. For the same $T_{c,PLLA} = 120$ °C, the PEO/PLLA blend with PEO composition greater than 25% exhibits ring-banded patterns even in uncovered sample. However, in much greater PEO composition (>80 wt %), uncovered samples exhibit ring bands diverging into dendritic patterns, while top covered samples tend to maintain the spiral ring-band patterns.

Chapter three

Materials & methods

3.1 METHODS

3.1.1 Excipients collection

For the purpose of experimentation of our research work, we offered the East West University, Dhaka-1219, Bangladesh; to give as some research grant. Our respected supervisors then sent a requisition letter to the authority for some specific recipients. After then we got different classes of excipients from the different labs of Pharmacy Dept. of East West University.

3.1.2 List of excipients

The list of excipients those were used during this research is given below

Table 3.1: Samples used in the experiment including source

Serial no.	Name of Excipients	Source (Supplier Name)
1.	Starch	MERK, Germany
2.	Zinc stearate	MERK, Germany
3.	Calcium phosphates	MERK, Germany
4.	Lactose	MERK, Germany
5.	Magnesium stearate	MERK, Germany
6.	Carboxymethyl Cellulose (CMC)	MERK, Germany
7.	Polyvinyl pyrrolidone (PVP)	MERK, Germany
8.	Polyethylene glycol (PEG)	MERK, Germany
9.	Talc	MERK, Germany

3.1.3 Equipments and Instruments

The equipments and instruments that were used in this experiment are mentioned below-

Table 3.2: List of instruments through this research work including source

Serial No.	Equipments	Source (Supplier Name)	Origin
1	Electronic Balance	Shimadzu AY220	Japan
2	Mixture Machine	Locally Produced	Bangladesh
3	Weight Balance	SHIMADZU	Japan

3.1.4 Images of Instruments

Some of the important instruments those were used during research work

Figure 3.1: Electronic Balance

Figure 3.2: Mixture Machine

3.1.5 Apparatus

Some technical equipment or machinery needed for a particular activity or research work. Apparatus may refer to machine, equipment and critical apparatus. Some apparatus are listed in the following table those were widely used throughout the experiments and research work.

Table 3.3: Apparatus used in this research

Serial no.	Apparatus
1	Test tube
2	Beaker
3	Measuring cylinder
4	Aluminum foil paper
5	Transparent tracing paper
6	Mortar & Pestles
7	Plastic container
8	Glass and plastic Funnel

9	Stand
10	Spatula
11	Glassrod
12	Masking Tap

3.2 METHOD

3.2.1 Methods in determining the angle of repose:

Tilting box method

This method is appropriate for fine-grained, non-cohesive materials, with individual particle size less than 10 mm. The material is placed within a box with a transparent side to observe the granular test material. It should initially be level and parallel to the base of the box. The box is slowly tilted at a rate of approximately 0.3 degrees/second. Tilting is stopped when the material begins to slide in bulk, and the angle of the tilt is measured.

Fixed funnel method

The material is poured through a funnel to form a cone. The tip of the funnel should be held close to the growing cone and slowly raised as the pile grows, to minimize the impact of falling particles. Stop pouring the material when the pile reaches a predetermined height or the base a predetermined width. Rather than attempt to measure the angle of the resulting cone directly, divide the height by half the width of the base of the cone. The inverse tangent of this ratio is the angle of repose.

Revolving cylinder method

The material is placed within a cylinder with at least one transparent face. The cylinder is rotated at a fixed speed and the observer watches the material moving within the rotating cylinder. The effect is similar to watching clothes tumble over one another in a slowly rotating clothes dryer. The granular material will assume a certain angle as it flows within the rotating cylinder. This method is recommended for obtaining the dynamic angle of repose, and may vary from the static angle of repose measured by other methods. When describing the angle of repose for a substance, always specify the method used.

3.2.2 Angle of Repose General Scale of Flow ability

By using the angle of repose, there is some variation in the qualitative description of powder flow properties. The classification of Carr: This is shown in Table 1. There are examples in the formulations with an angle of repose in the range of 40° to 500 that were manufactured satisfactorily, when the angle of repose exceeds 500. The

flow is rarely acceptable for manufacturing purposes (USP29-NF24, 2013).

3.2.2.1 Some Considerations for Angle of Repose

The properties of the powder is not an intrinsic in angle of repose i.e. It is dependent upon the method used to form the cone of powder. The following important considerations are:

• By carefully building the powder cone because the peak of the cone of powder can be distorted by the impact of powders from above.

• The nature of the base upon which the powder cone is formed that is influenced by the angle of repose. It is recommended that the powder cone be formed on a “common base”, which can be achieved by forming the cone of powder on a layer of powder. This can be done by using a base of fixed diameter with a protruding outer edge to

retain a layer of powder upon which the cone is formed (USP29-NF24, 2013).

3.2.2.2 Recommended Procedure for Angle of Repose

Form the angle of repose on a fixed base with a retaining lip to retain a layer of powder on the base.

- The base should not be vibrated.
- The height of the funnel is varied to carefully build up a symmetrical cone of powder.
- The vibration should be prevented when the funnel is moved.
- The funnel height should be maintained approximately 2-4 cm from the top of the powder pile.
- If a symmetrical cone of powder cannot be successfully prepared then this method is not appropriate.
- The determination of the angle of repose by measuring the

height of the cone of powder and calculate the angle of repose, α, from the following equation:

$$\tan(\alpha) = \frac{\text{height}}{0.5\ \text{base}}$$

Angle of Repose (α) is the maximum angle between the surfaces of a pile of powder and horizontal plane. It is usually determined by Fixed Funnel Method and is the measure of the flowability of powder/granules (USP29-NF24, 2013).

$$\alpha = \tan^{-1}(h / r)$$

Where, h = height of heap of pile

r = radius of base of pile

Table 3.4: Angle of Repose

ANGLE OF REPOSE	TYPE OF FLOW
< 25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very Poor

3.2.3 Some experimental Considerations for the Compressibility Index and Hausner Ratio

Compressibility index and Hausner ratio are not intrinsic properties of the powder; i.e., they depend on the methodology used. There are discussions of the following important considerations affecting the determination of

(1) The unsettled apparent volume, Vo,

(2) The final tapped volume, Vf,

(3) The bulk density, *P*bulk, and

(4) The tapped density, *P*tapped

Few things that were considered are,

- The diameter of the cylinder used
- The number of times the powder tapped to determine the tapped density
- The mass of material used in the test
- Rotation of the sample during tapping

3.2.4 Preparation of Formulas

3.2.4.1 Preparation of Formula (F1):

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

Table 3.5: Formulation of F1

Ingredients Name	Purpose of Use	Percentage	Quantity
Starch	Diluent	45%	4.5
Carboxy methylcellulose	Disintegrant	25%	2.5
Zinc Stearate	Antiadherent	15%	1.5
Talc	Lubricant	15%	1.5
		Total=100%	Total=10g

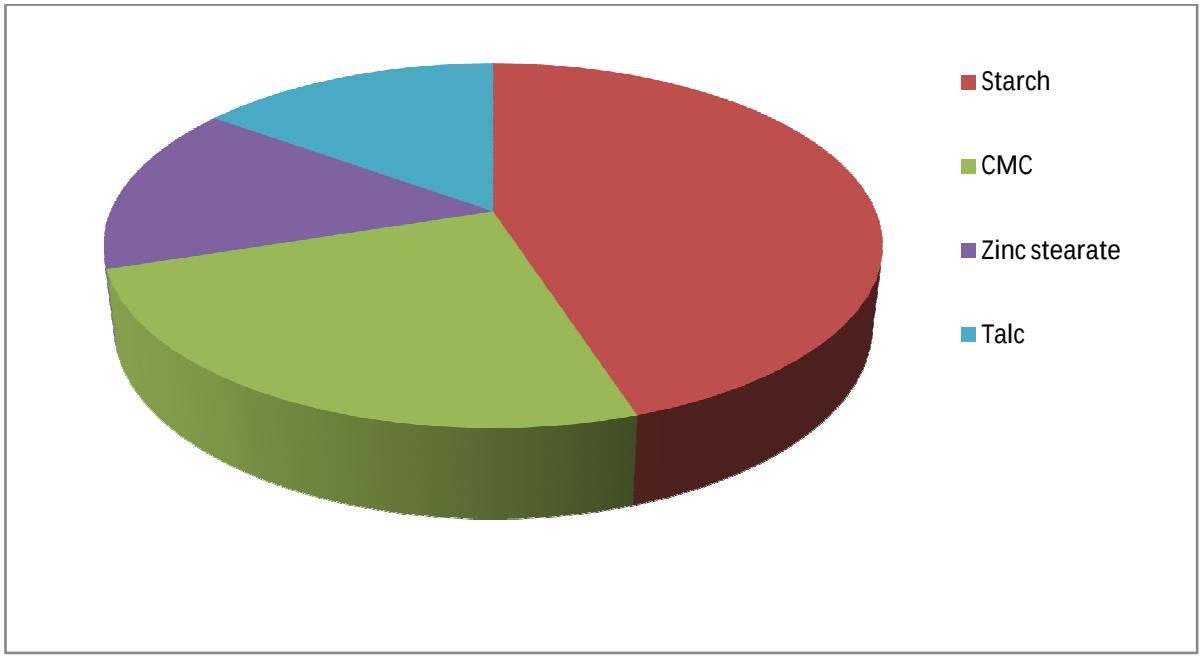

Figure 3.3: Pie diagram of F1

3.2.4.2 Process of measuring Bulk Volume

- Mixture was taken in a 25ml measuring cylinder.
- The upper level of the powder was taken as a measurement of bulk volume.
- This process was performed three times
- An average of three determinations was considered as a bulk volume

3.2.4.3 Process of measuring Tapped Volume

- Mixture was taken in a 25ml measuring cylinder.
- Then the measuring cylinder was tapped 30 times.
- The lower level of the powder was taken as a measurement of tapped volume
- This process was performed three times.
- An average of three determinations was considered as a bulk volume.

3.2.4.4 Process of measuring Angle of Repose

- Plastic or glass funnel was attached to a stand
- 5gm mixture was poured through the orifice of the funnel
- The radius and the height of the peak was determined.
- This process was performed three times.
- An average of three determinations was considered as the measurement.

3.3.1 Preparation of Set-1:

After preparing 10g of F1, specific binder was mixed with it in different fixed and justified ratio. For this formula, PEG was used. The required amount of both PEG and F1 was calculated for preparing each 3g of mixture in five different ratios. A total of four of sample mixture of 3g were set up for further procedure that is the determination of flow property

Table 3.6: The amount of PEG and F1 in different ratio (Set-1) in 3g.

Ratio	PEG : F1	Amount of PEG : F1 (in g)
1	10% : 90%	0.30 : 2.70
2	11% : 89%	0.33: 2.67
3	12% : 88%	0.36 : 2.64
4	15% : 85%	0.45 : 2.55

3.3.2 Preparation of Set-2:

Table 3.7: Formulation of F2

Ingredients Name	Purpose of Use	Percentage	Quantity
Starch	Diluent	45%	4.5
Carboxy methylcellulose	Disintegrant	25%	2.5
Zinc Stearate	Antiadherent	15%	1.5
Talc	Lubricant	15%	1.5
		Total=100%	Total=10g

After preparing 10g of F2, the required amount of both PEG and F2 was calculated for preparing each 3g of mixture in four different ratios. A total of five of sample mixture of 3g were set up for further procedure that is the determination of flow property

Table 3.8: The amount of PEG and F2 in different ratio (Set-2) in 3g.

Ratio	PEG : F2	Amount of PVP : F2 (in g)
1	8% : 92%	0.24 : 2.76
2	12% : 88%	0.36 : 2.70
3	15% : 85%	0.45 : 2.55
4	17% : 83%	0.51 : 2.49
5	20% : 80%	0.60 : 2.40

3.3.3 Preparation of Set-3

Table 3.9: Formulation of F3

Ingredients Name	Purpose of Use	Percentage	Quantity
Starch	Diluent	45%	4.5
Carboxy methylcellulose	Disintegrant	25%	2.5
Zinc Stearate	Antiadherent	15%	1.5
Talc	Lubricant	15%	1.5
		Total=100%	Total=10g

After preparing 10g of F3, the required amount of both PEG and F3 was calculated for preparing each 3g of mixture in five different ratios. A total of four of sample mixture of 3g were set up for further procedure that is the determination of flow property

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

Ratio	PEG : F3	Amount of PEG : F3 (in g)
1	20% : 80%	0.60 : 2.40
2	21% : 79%	0.63 : 2.37
3	22% : 78%	0.66 : 2.34
4	23% : 77%	0.69 : 2.31
5	25%:75%	0.75 : 2.25

3.3.4 Preparation of Set-4:

- Each ratio of the set-1 was divided to two equal portions.
- Each portion contains about 1.5 g of mixture.
- Amlodipine was added to each ratio of set-1.
- Assuming that 80 mg of amlodipine tablet contain 5 mg of amlodipine. So, 1.4 g or 1400 mg contain 87.5 mg or .0875 g of amlodipine.

3.3.5 Preparation of Set-5 (For Amlodipine):

- Each ratio of the set-2 was divided to two equal portions.
- Each portion contains about 1.5 g of mixture.
- Amlodipine was added to each ratio of set-2.
- Assuming that 80 mg of amlodipine tablet contain 5 mg of amlodipine. 1.4 g or 1400 mg contain 87.5 mg or .0875 g of amlodipine.

3.3.6 Preparation of Set-6 (For Amlodipine):

- Each ratio of the set-3 was divided to two equal portions.
- Each portion contains about 1.5 g of mixture.
- Amlodipine was added to each ratio of set-3.
- Assuming that 80 mg of amlodipine tablet contain 5 mg of amlodipine. 1.4 g or 1400 mg contain 87.5 mg or .0875 g of amlodipine.

3.3.7 Preparation of Set-7 (For Propranolol):

- Each ratio of the set-1 was divided to two equal portions.
- Each portion contains about 1.5 g of mixture.
- Propranolol was added to each ratio of set-1.
- Assuming that 80 mg of amlodipine tablet contain 5 mg of amlodipine. 1.4 g or 1400 mg contain 87.5 mg or .0875 g of amlodipine

3.3.8 Preparation of Set-8 (For Propranolol):

- Rest of the portion of set-2 was taken
- The portion contains about 1.5g of mixture.
- Propanolol HCl was added to each ratio of set-2.
- Assuming that 80 mg of Propanolol HCl tablet contain 5mg of Propanolol HCl .so, 1.4 g or 1400 mg contain 87.5 mg or .0875 g of Propanolol HCl

3.3.9 Preparation of Set-9 (For Propranolol):

- Rest of the portion of set-3 was taken
- The portion contains about 1.5g of mixture.
- Propanolol HCl was added to each ratio of set-3.
- Assuming that 80 mg of Propanolol HCl tablet contain 5mg of Propanolol HCl .so, 1.4 g or 1400 mg contain 87.5 mg or .0875 g of Propanolol HCl

Chapter four

Result

Determination of variation in Flow Property of Different Formulas of PEG (Polyethylene Glycol) along with Amlodipine and Propranolol

4.1.1 For SET- 1(Excipient with PEG): For calculating Carr's index and Hausner ratio, their individual bulk volume and tapped volume were measured three times and the average value was taken. The observed value is given below

Table 4.1: Carr's index and Hausner Ratio for different ratios of set-1 and PEG

Ratio	Bulk Volume, Vo (ml)	Most Acceptable Value of Vo (ml)	Tapped Volume, Vr (ml)	Most Acceptable value of Vr (ml)	Hausner's Ratio	Compressibility index
1	7.5 7.2 7.5	7.4	4.9 5.5 5.1	5.2	1.42	29.72
2	7.5 7 7.5	7.3	4.5 4.8 4.2	4.5	1.64	38.19
3	6.8 6.5 6.8	6.7	3.9 3.6 4.5	4.02	1.68	41.30
4	6.50 5.50 6.00	6.6	3.9 3.6 3.9	3.76	1.75	43.03
5	5.50 6.00 6.00	6.5	3.6 3.00 3.3	3.4	1.98	47.69

Table 4.2: Angle of Repose for different mixtures of set-1 and PEG

Ratio	Height (h) (cm)	Average Height,(h) (cm)	Diameter (2r) (cm)	Average Diameter(2r) (cm)	Radius (r) (cm)	Angle of Repose (^{0})
1	1.08	1.07	2.94	3	1.5	35.50
	1.05		3			
	1.08		3.1			
2	1.32	1.3	2.9	2.8	1.4	42.88
	1.26		2.8			
	1.32		2.8			
3	1.3	1.4	2.76	2.7	1.4	45
	1.3		2.7			
	1.2		2.7			
4	1.44	1.6	2.7	2.6	1.3	50.90
	1.38		2.5			
	1.44		2.7			
5	1.8	1.8	2.5	2.5	1.4	52.13
	1.7		2.7			
	1.8		2.5			

4.1.2 SET- 2(Excipient with PEG):

For calculating Carr's index and Hausner ratio, their individual bulk volume and tapped volume were measured three times and the average value was taken. The observed value is given below:

Table 4.3: Carr's index and Hausner Ratio for different ratios of set-2 and PEG

Ratio	Bulk Volume, Vo (ml)	Most Acceptable Value of Vo (ml)	Tapped Volume, Vr (ml)	Most Acceptable value of Vr (ml)	Hausner's Ratio	Compressibility index
8% : 92%	5.1	5.2	4.20	4.40	1.14	15.38
	5.4		4.50			
	5.1		4.50			
12% : 88%	5.1	4.9	4.50	4.3	1.18	21.25
	4.8		4.00			
	4.8		4.20			
15% : 85%	5.1	4.8	4.20	4.00	1.2	26.67
	4.6		3.9			
	4.6		3.9			
17% :83%	4.3	4.9	3.60	3.48	1.40	28.97
	5		4.00			
	4.3		3.60			
20% : 80%	5.1	4.3	3.30	3.18	1.45	36.04
	4		3.30			
	4		3.00			

Table 4.4: Angle of Repose for different mixtures of set-2 and PEG

Ratio	Height (h) (cm)	Average Height (h) (cm)	Diameter (2r) (cm)	Average Diameter (2r) (cm)	Radius (r) (cm)	Angle of Repose (^{0})
1	1.2	1.4	1.9	2.1	1.05	33.69
	1.5		2			
	1.5		2.5			
2	1.3	1.5	2.9	2.7	1.4	46.97
	1.6		2.7			
	1.6		2.7			
3	1.7	1.8	2.6	2.8	1.4	52.12
	1.8		3			
	1.8		3			
4	2.1	2.2	2.5	2.6	1.3	59.42
	2.2		2.5			
	2.2		2.7			
5	1.9	2.1	2.9	2.8	1.4	56.31
	2.1		2.7			
	2.1		2.9			

4.1.3 SET-3(Excipient with PEG): For calculating Carr's index and Hausner ratio, their individual bulk volume and tapped volume were measured three times and the average value was taken. The observed value is given below

Table 4.5: Carr's index and Hausner Ratio for different ratios of set-3 and PEG

Ratio	Bulk Volume, Vo (ml)	Most Acceptable Value of Vo (ml)	Tapped Volume, Vr (ml)	Most Acceptable value of Vr (ml)	Hausner's Ratio	Compressibility index
1	5.6 5.4 5.6	5.2	4.20 4.50 4.50	4.40	1.18	14.10
2	5.4 4.8 4.8	5	4.50 4.00 4.20	4.30	1.2	15.48
3	5.1 4.8 4.9	4.8	4.20 3.9 3.9	4.00	1.28	16.66
4	4.8 5 4.5	4.7	3.60 3.50 3.60	3.5	1.3	25.53
5	5.1 4 4	4.4	3.30 3.30 3.00	3.1	1.42	29.54

Table 4.6: Angle of Repose for different mixtures of set-3 and PEG

Ratio	Height (h) (cm)	Average Height,(h) (cm)	Diameter (2r) (cm)	Average Diameter (2r) (cm)	Radius (r) (cm)	Angle of Repose (^{0})
1	1.3	1.4	1.9	2.2	1.1	44.84
	1.5		2.1			
	1.5		2.5			
2	1.4	1.5	2.7	2.7	1.3	49.08
	1.6		2.9			
	1.6		2.7			
3	1.7	1.8	2.8	2.8	1.4	52.12
	1.8		3			
	1.8		3			
4	2.2	2.2	3.1	3	1.5	53.71
	2.2		3.1			
	2.2		2.8			
5	2.5	2.3	2.9	3.1	1.6	55.17
	2.1		3.4			
	2.1		2.9			

4.1.4 SET-4 (Amlodipine with set-1): For calculating Carr's index and Hausner ratio, their individual bulk volume and tapped volume were measured three times and the average value was taken. The observed value is given below:

Table 4.7: Carr's index and Hausner Ratio for different ratios of set-4 and Amlodipine

Ratio	Bulk Volume, Vo (ml)	Most Acceptable Value of Vo (ml)	Tapped Volume, Vr (ml)	Most Acceptable value of Vr (ml)	Hausner's Ratio	Compressibility index
1	5.00 5.00 6.00	5.3	3.00 3.50 4.00	3.5	1.53	33.96
2	5.0 4.8 5.0	4.9	3.50 2.50 3.20	3.1	1.59	36.76
3	4.6 4.6 4.8	4.7	3.20 3.00 2.5	2.9	1.62	38.29
4	4.8 4.4 4.2	4.3	2.20 2.50 2.20	2.3	1.87	46.51
5	4.5 4.2 4.2	4.1	2.00 2.50 2.00	2.1	1.96	48.78

Table 4.8: Angle of Repose for different mixtures of set-4 and Amlodipine

Ratio	Height (h) (cm)	Average Height (h) (cm)	Diameter (2r) (cm)	Average Diameter (2r) (cm)	Radius (r) (cm)	Angle of Repose (^{0})
1	1.3	1.4	2.9	3.03	1.5	43.03
	1.4		3.1			
	1.4		3.1			
2	1.5	1.6	2.8	2.8	1.4	48.81
	1.5		2.8			
	1.8		2.6			
3	1.6	1.7	2.8	2.7	1.35	51.55
	1.6		2.7			
	1.8		2.7			
4	1.7	1.8	2.7	2.6	1.3	54.16
	1.7		2.5			
	1.8		2.7			
5	1.9	2.1	2.0	2.4	1.2	60.25
	2.1		2.7			
	2.1		2.5			

4.1.5 SET-5 (Amlodipine with set-2): For calculating Carr's index and Hausner ratio, their individual bulk volume and tapped volume were measured three times and the average value was taken. The observed value is given below

Table 4.9: Carr's index and Hausner Ratio for different ratios of set-5 and Amlodipine

Ratio	Bulk Volume, Vo (ml)	Most Acceptable Value of Vo (ml)	Tapped Volume, Vr (ml)	Most Acceptable value of Vr (ml)	Hausner's Ratio	Compressibility index
8% : 92%	4.1 4.4 5.1	4.5	3.50 4.20 4.50	4.06	1.02	9.70
12% : 88%	4.1 4.5 4.5	4.4	3.50 4.00 4.00	3.8	1.15	13.63
15% : 85%	4.5 4 4.6	4.3	3.8 3.6 3.5	3.6	1.20	16.37
17% :83%	4.3 4 4.3	4.2	3.60 4.00 3.60	3.4	1.28	19.04
20% : 80%	4.6 3.8 4	4.1	3.30 3.30 3.00	3.1	1.32	24.49

Table 4.10: Angle of Repose for different mixtures of set-5 and Amlodipine

Ratio	Height (h) (cm)	Average Height (h) (cm)	Diameter (2r) (cm)	Average Diameter (2r) (cm)	Radius (r) (cm)	Angle of Repose (^{0})
1	1.5	1.5	2.9	2.8	1.4	46.97
	1.4		2.9			
	1.5		2.7			
2	1.5	1.6	2.9	2.7	1.3	50.90
	1.6		2.7			
	1.7		2.7			
3	1.7	1.8	2.6	2.5	1.2	56.31
	1.8		2.5			
	1.9		2.6			
4	2.2	2.3	2.5	2.3	1.15	63.43
	2.5		2.2			
	2.2		2.2			
5	2.5	2.4	2.0	2.03	1.02	66.97
	2.6		2.2			
	2.1		1.9			

4.1.6 SET-6 (Amlodipine with set-3): For calculating Carr's index and Hausner ratio, their individual bulk volume and tapped volume were measured three times and the average value was taken. The observed value is given below

Table 4.11: Carr's index and Hausner Ratio for different ratios of set-6 and Amlodipine

Ratio	Bulk Volume, Vo (ml)	Most Acceptable Value of Vo (ml)	Tapped Volume,Vr (ml)	Most Acceptable value of Vr (ml)	Hausner's Ratio	Compressibility index
20% : 80%	4.6 5.4 5.2	5.1	4.5 4.0 4.2	4.2	1.21	17.65
21% : 79%	5.0 4.8 4.8	4.8	3.8 3.8 3.8	3.8	1.37	22.83
22% : 78%	5.1 4.6 4.6	4.7	3.1 3.5 3.1	3.2	1.47	31.91
23% :77%	4.5 4.2 4.5	4.4	3.10 2.50 3.10	2.9	1.52	34.09
25% : 75%	4.5 4 4	4.1	3.00 2.50 2.50	2.6	1.58	37.58

Table 4.12: Angle of Repose for different mixtures of set-6 and Amlodipine

Ratio	Height (h) (cm)	Average Height (h) (cm)	Diameter (2r) (cm)	Average Diameter (2r) (cm)	Radius (r) (cm)	Angle of Repose (^{0})
1	1.2	1.1	2.9	3.1	1.55	35.36
	1.2		2.5			
	1.1		3.5			
2	1.4	1.4	2.9	2.7	1.35	46.04
	1.2		2.5			
	1.5		2.7			
3	1.9	2.0	2.8	2.5	1.25	57.99
	1.8		2.5			
	2		2.5			
4	2.2	2.3	2.4	2.3	1.15	61.43
	2.5		2.4			
	2.2		2.1			
5	2.5	2.6	1.9	2	1.0	63.17
	2.4		2.0			
	2.5		2.1			

4.1.7 SET-7 (Propranolol with set-1)

For calculating Carr's index and Hausner ratio, their individual bulk volume and tapped volume were measured three times and the average value was taken. The observed value is given below:

Table 4.13: Carr's index and Hausner Ratio for different ratios of set-7 and Propranolol

Ratio	Bulk Volume, Vo (ml)	Most Acceptable Value ofVo (ml)	Tapped Volume,Vr (ml)	Most Acceptable value of Vr (ml)	Hausner's Ratio	Compressibility index
1	4.8 4.5 4.9	4.7	3.00 4.00 3.20	3.4	1.38	27.66
2	4.5 4.2 4.2	4.3	3.00 3.50 3.20	3.0	1.38	30.24
3	4.6 4.0 3.8	4.1	3.00 3.00 2.50	2.8	1.48	32.70
4	3.8 4.0 3.8	3.8	2.20 2.50 2.20	2.3	1.65	39.47
5	3.8 4.0 3.5	3.6	2.30 2.20 2.20	2.1	1.71	41.67

Table 4.14: Angle of Repose for different mixtures of set-7 and Propranolol

Ratio	Height (h) (cm)	Average Height (h) (cm)	Diameter (2r) (cm)	Average Diameter (2r) (cm)	Radius (r) (cm)	Angle of Repose (^{0})
1	1.5	1.6	3.1	2.9	1.4	48.81
	1.4		2.8			
	1.8		2.8			
2	1.5	1.7	2.5	2.5	1.25	53.67
	1.8		2.5			
	1.8		2.6			
3	1.9	2.0	2.5	2.2	1.1	61.18
	2.2		2.1			
	1.8		2.1			
4	2.2	2.3	2.1	2.03	1.015	66.18
	2.5		2.0			
	2.2		2.0			
5	2.9	2.6	2.0	1.9	0.95	69.92
	2.5		1.9			
	2.5		1.8			

4.1.8 SET-8 (Propranolol with set-2): For calculating Carr's index and Hausner ratio, their individual bulk volume and tapped volume were measured three times and the average value was taken. The observed value is given below

Table 4.15: Carr's index and Hausner Ratio for different ratios of set-8 and Propranolol

Ratio	Bulk Volume, Vo (ml)	Most Acceptable Value ofVo (ml)	Tapped Volume,Vr (ml)	Most Acceptable value of Vr (ml)	Hausner's Ratio	Compressibility index
1	4.5 4.5 4.1	4.4	3.50 3.20 3.50	3.4	1.29	22.72
2	4.1 4.1 4.5	4.2	3.50 3.00 3.00	3.2	1.38	23.80
3	4.2 4 4.2	4.13	2.9 3.0 3.0	2.9	1.42	29.78
4	4.3 4 4	4.06	3.20 2.50 2.20	2.6	1.56	35.96
5	3.8 3.8 4	3.8	2.30 2.30 2.50	2.36	1.61	37.89

Table 4.16: Angle of Repose for different mixtures of set-8 and Propranolol

Ratio	Height (h) (cm)	Average Height (h) (cm)	Diameter (2r) (cm)	Average Diameter (2r) (cm)	Radius (r) (cm)	Angle of Repose (^{0})
1	1.2	1.26	3.1	3.03	1.515	39.75
	1.4		2.9			
	1.2		3.1			
2	1.4	1.56	2.9	2.83	1.415	47.79
	1.6		2.7			
	1.7		2.9			
3	1.9	1.86	2.6	2.43	1.215	56.84
	1.8		2.5			
	1.9		2.2			
4	2.1	2.06	2.2	2.1	1.05	62.99
	2.2		2.2			
	1.9		2			
5	2.2	2.3	2.0	1.93	0.965	67.24
	2.5		1.9			
	2.2		1.9			

4.1.9 SET-9 (Propranolol with set-3): For calculating Carr's index and Hausner ratio, their individual bulk volume and tapped volume were measured three times and the average value was taken. The observed value is given below

Table 4.17: Carr's index and Hausner Ratio for different ratios of set-9 and Propranolol

Ratio	Bulk Volume, Vo (ml)	Most Acceptable Value ofVo (ml)	Tapped Volume,Vr (ml)	Most Acceptable value of Vr (ml)	Hausner's Ratio	Compressibility index
1	4.8 5.6 5.6	5.4	4.2 4.0 4.0	4.06	1.33	17.65
2	5.0 5.2 5.2	5.1	3.8 3.5 3.5	3.6	1.42	22.83
3	4.8 4.6 4.5	4.6	3.0 3.2 3.0	3.06	1.51	31.91
4	4.5 4.4 4.1	4.3	3.10 2.50 2.50	2.7	1.59	37.21
5	4.2 4 4	4.06	2.50 2.30 2.30	2.36	1.72	41.87

Table 4.18: Angle of Repose for different mixtures of set-9 and Propranolol

Ratio	Height (h) (cm)	Average Height (h) (cm)	Diameter (2r) (cm)	Average Diameter (2r) (cm)	Radius (r) (cm)	Angle of Repose (^{0})
1	1.2	1.26	3.1	3.2	1.6	38.22
	1.2		3.1			
	1.4		3.5			
2	1.5	1.53	2.9	2.76	1.38	47.95
	1.4		2.7			
	1.7		2.7			
3	1.9	1.97	2.8	2.5	1.25	57.60
	2.0		2.5			
	2.0		2.2			
4	2.2	2.4	2.4	2.23	1.115	65.08
	2.5		2.2			
	2.5		2.1			
5	2.5	2.57	1.9	1.93	0.965	69.41
	2.4		2.0			
	2.8		1.9			

4.2 Comparison shown using graph among 3 types (excipients, amlodipine, propranolol) of different sets of Formulas (Set-1, Set-2, Set-3) on the basis of Carr's index, Hausner ratio, and Angle of repose

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

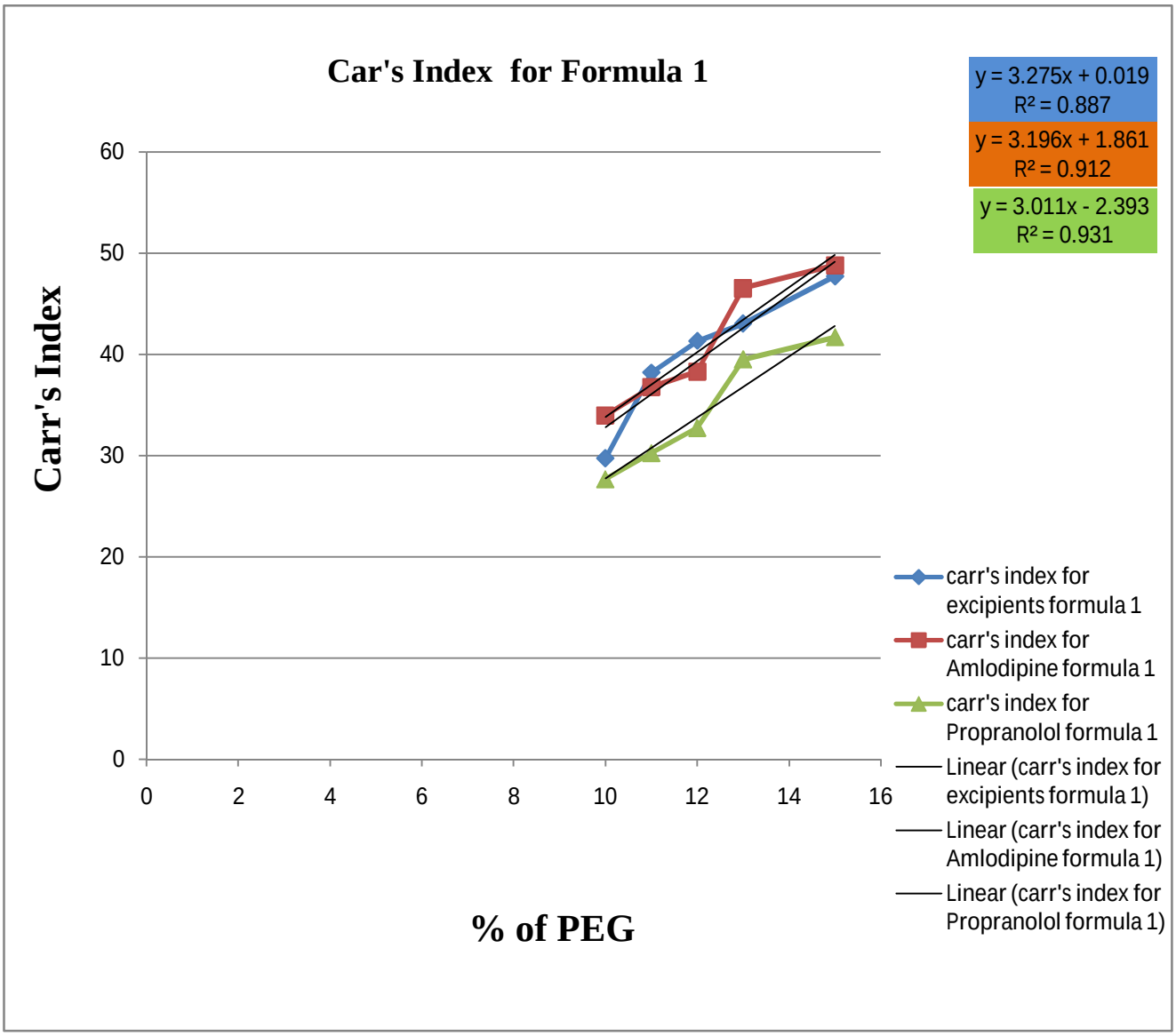

Figure 4.1(a): A percentage ratio of PEG versus Carr's Index graph (Formula 1)

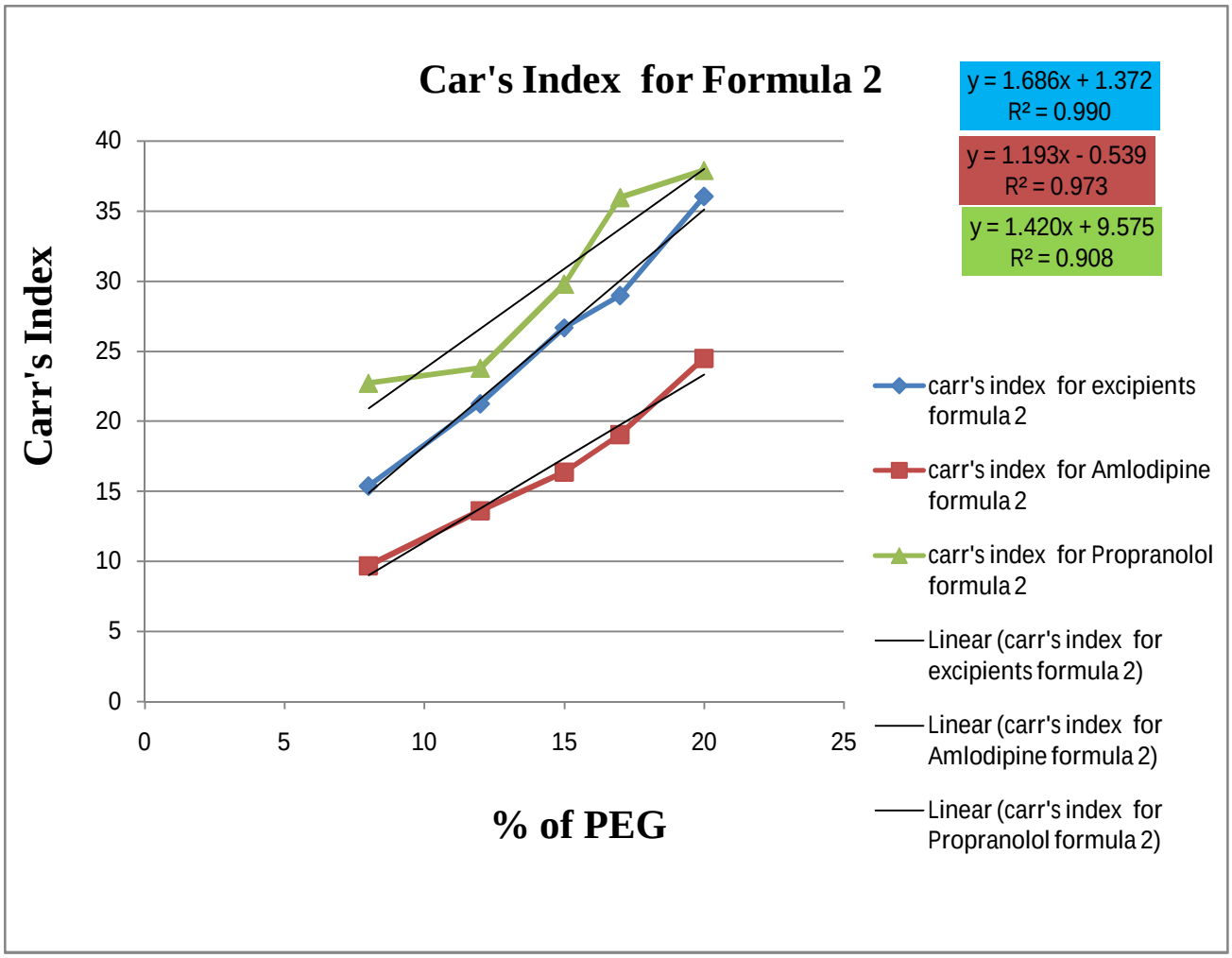

Figure 4.2(a): A percentage ratio of PEG versus Carr's Index graph (Formula 2)

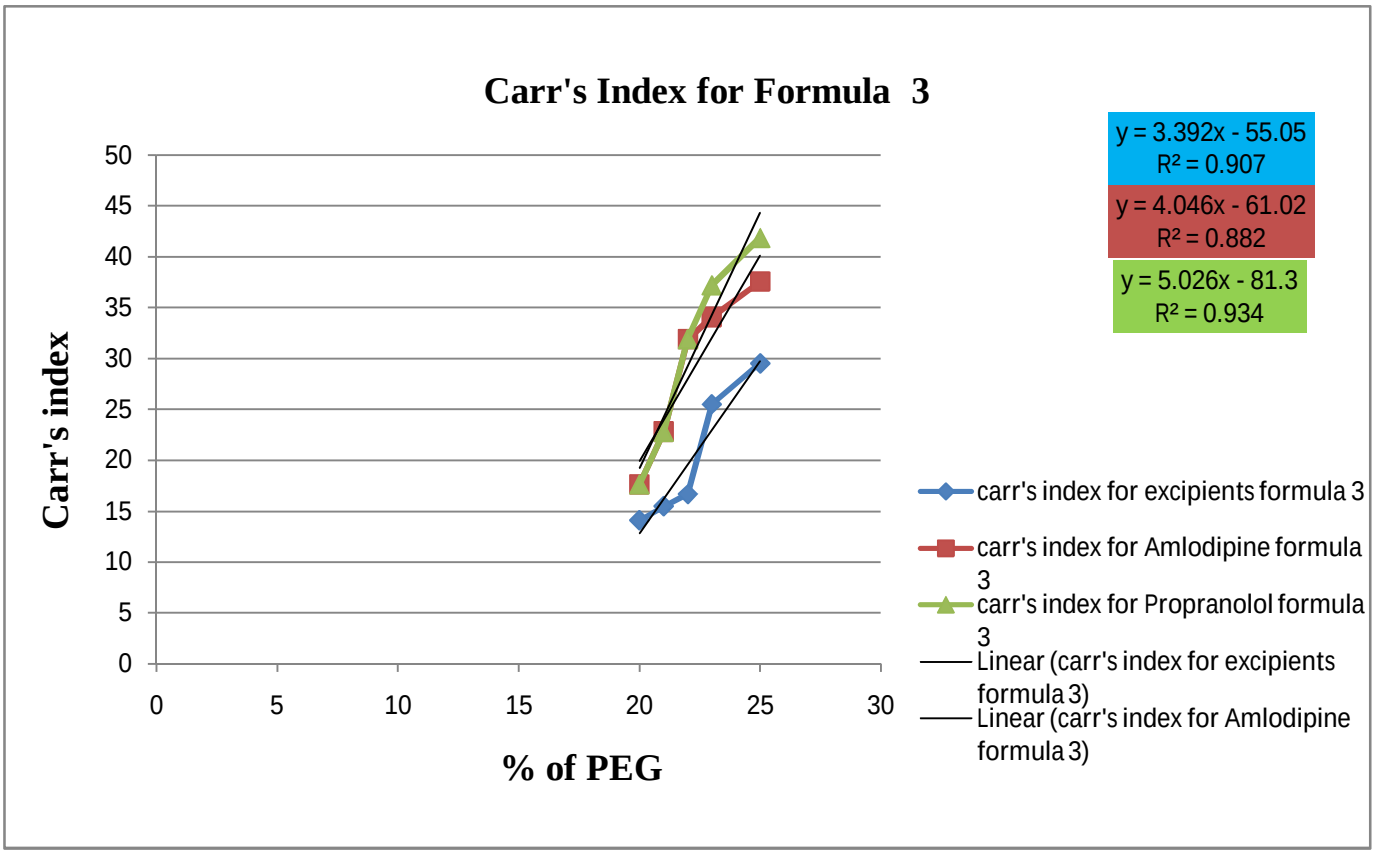

Figure 4.3(a): A percentage ratio of PEG versus Carr's Index graph (Formula 3)

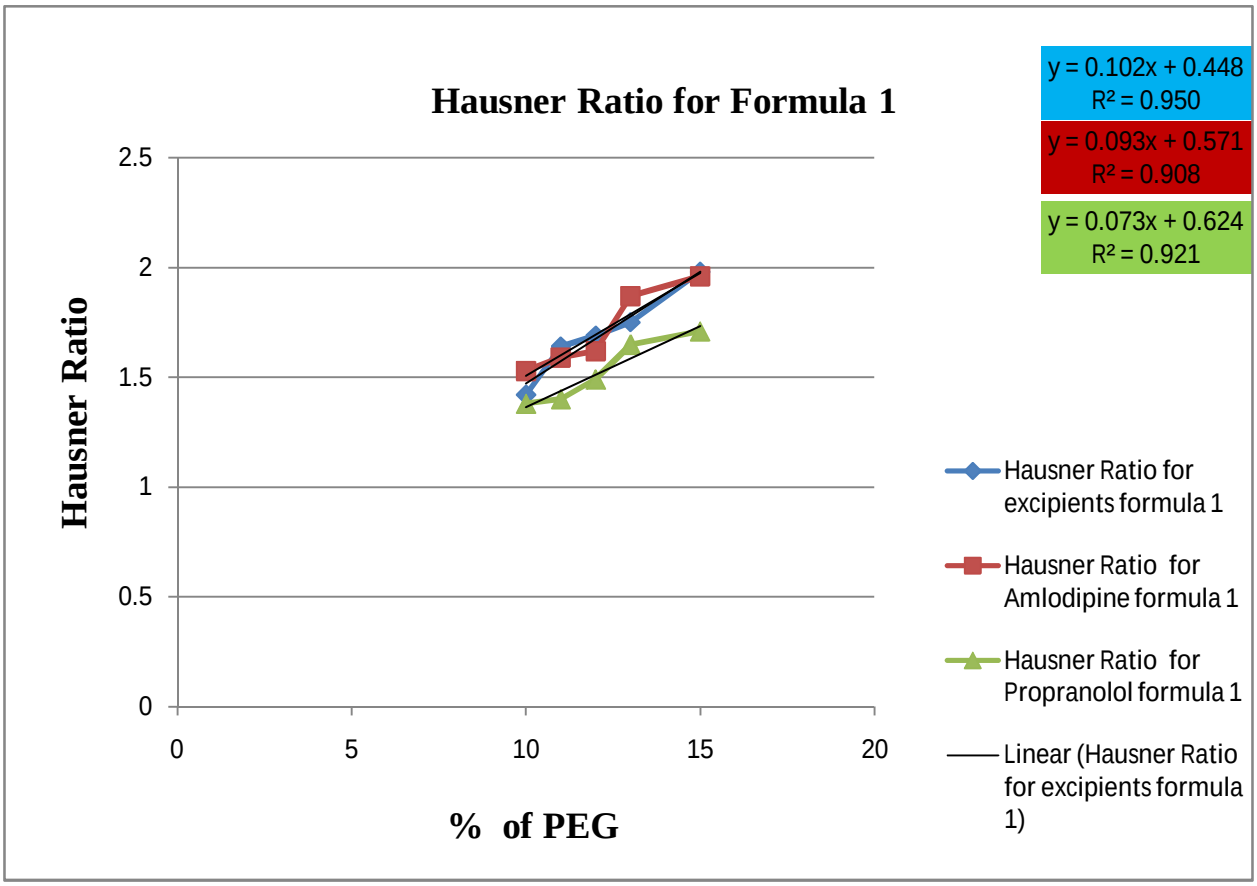

Figure 4.1(b): A percentage ratio of PEG versus Hausner ratio graph (Formula 1)

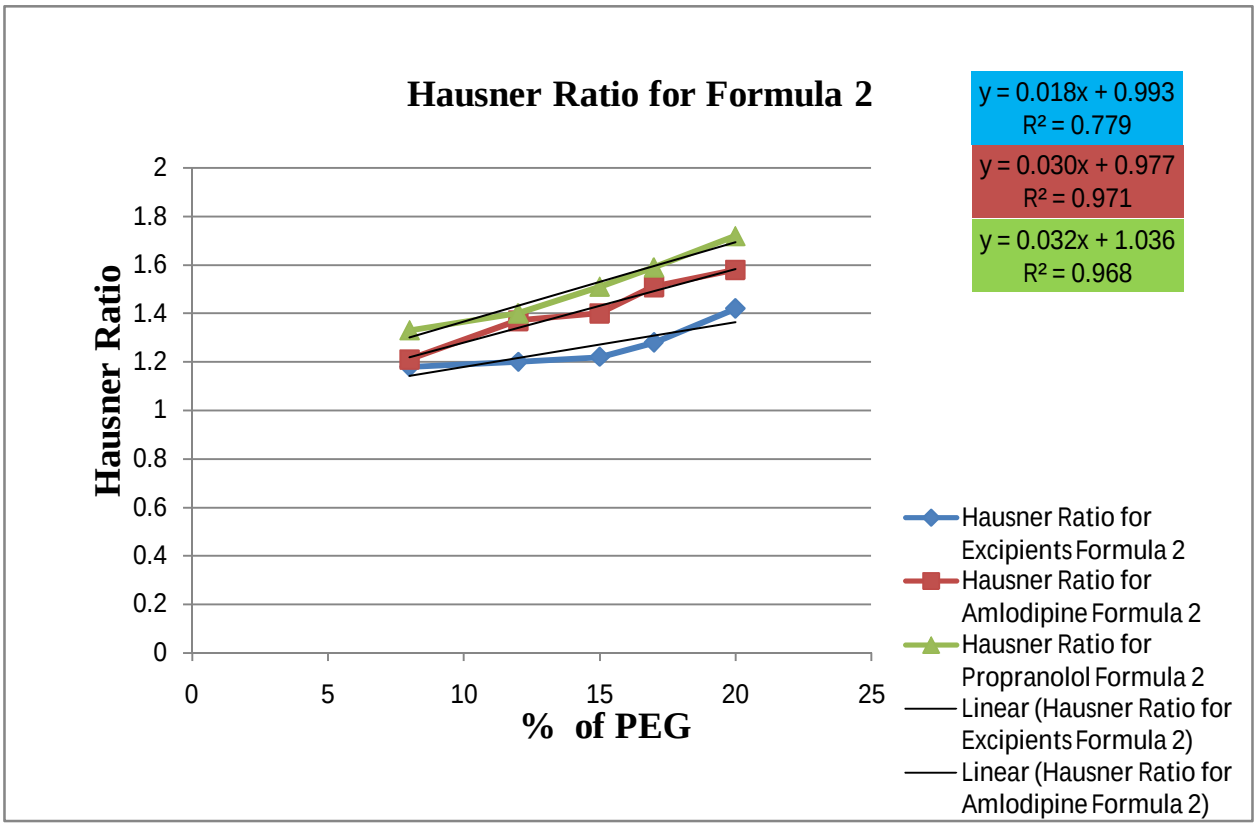

Figure 4.2(b): A percentage ratio of PEG versus Hausner ratio graph (Formula 2)

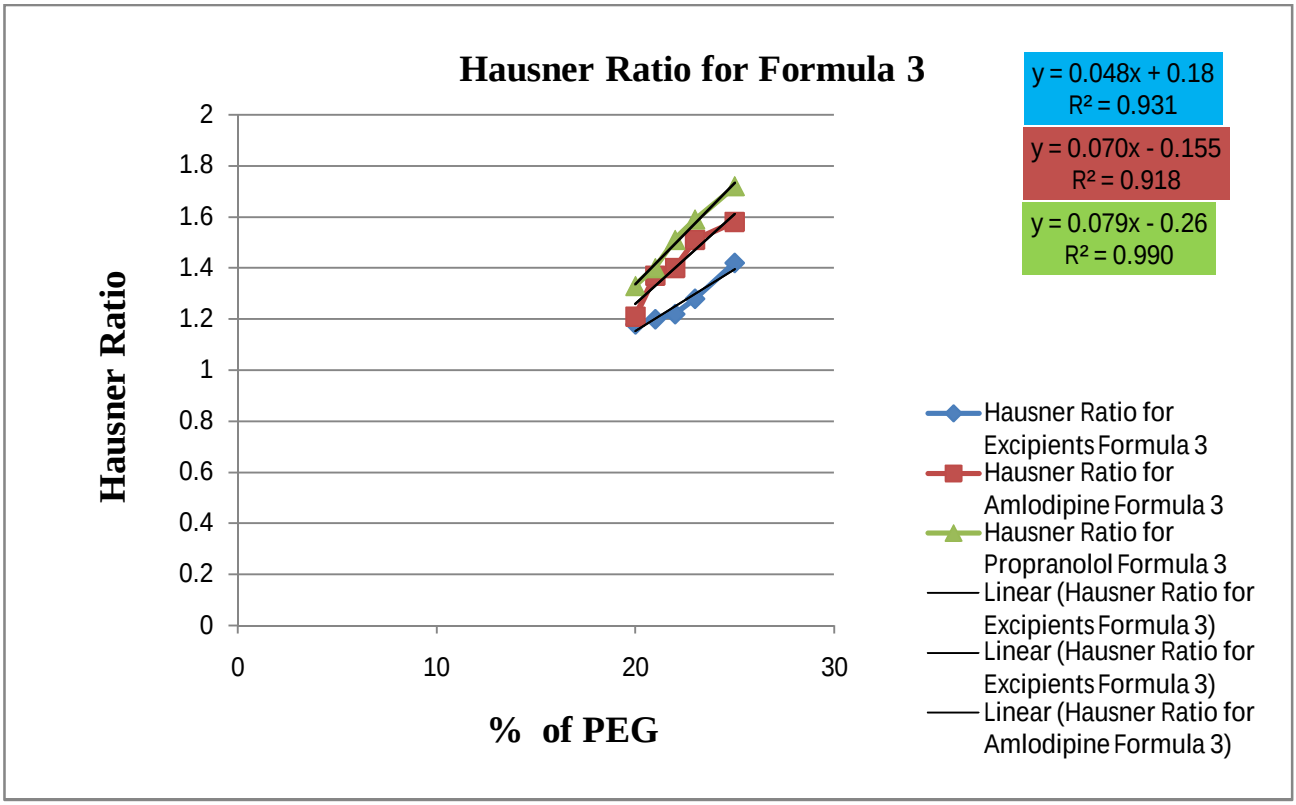

Figure 4.3(b): A percentage ratio of PEG versus Hausner ratio graph (Formula 3)

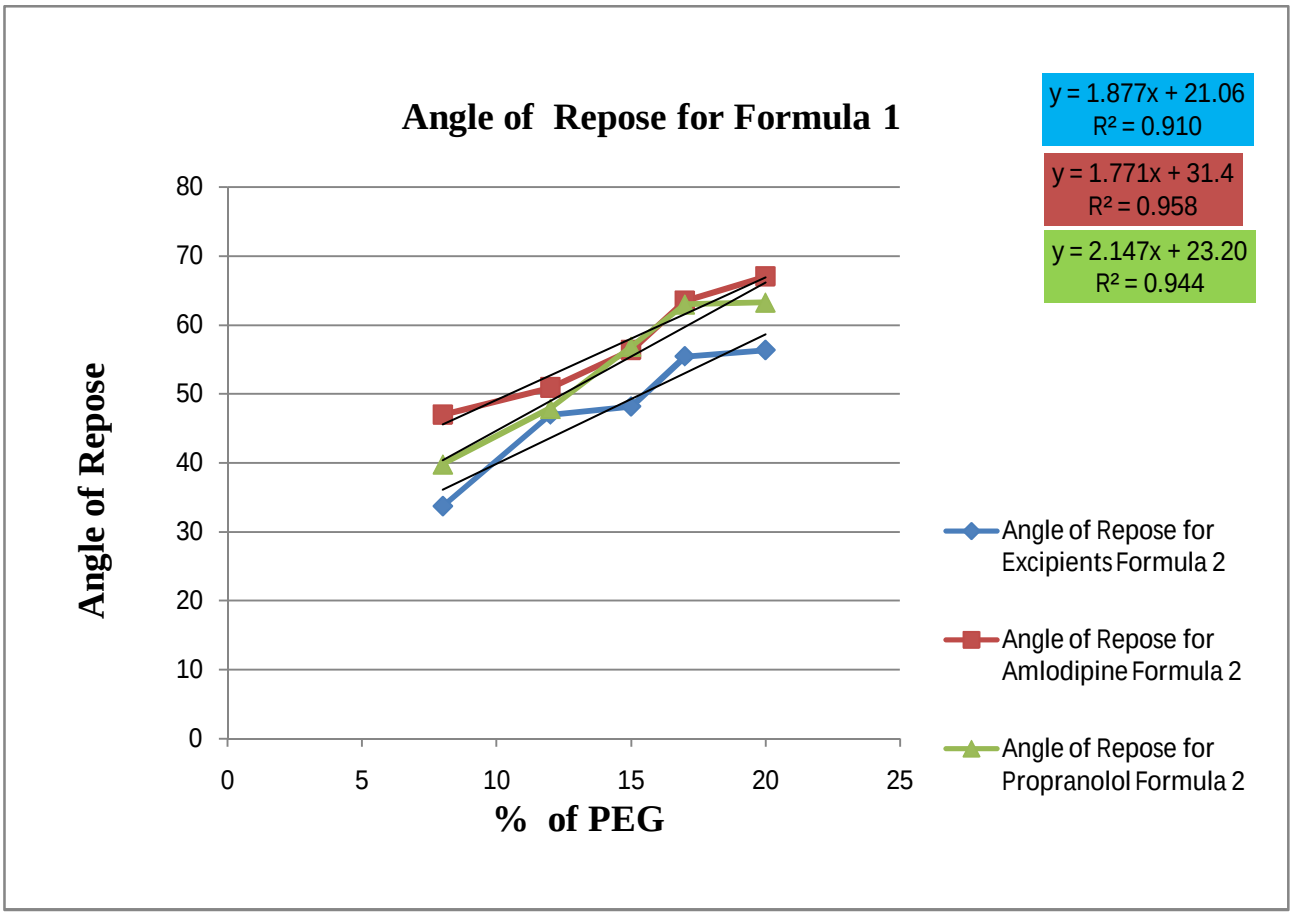

Figure 4.1(c): A percentage ratio of PEG versus Angle of repose graph (Formula 1)

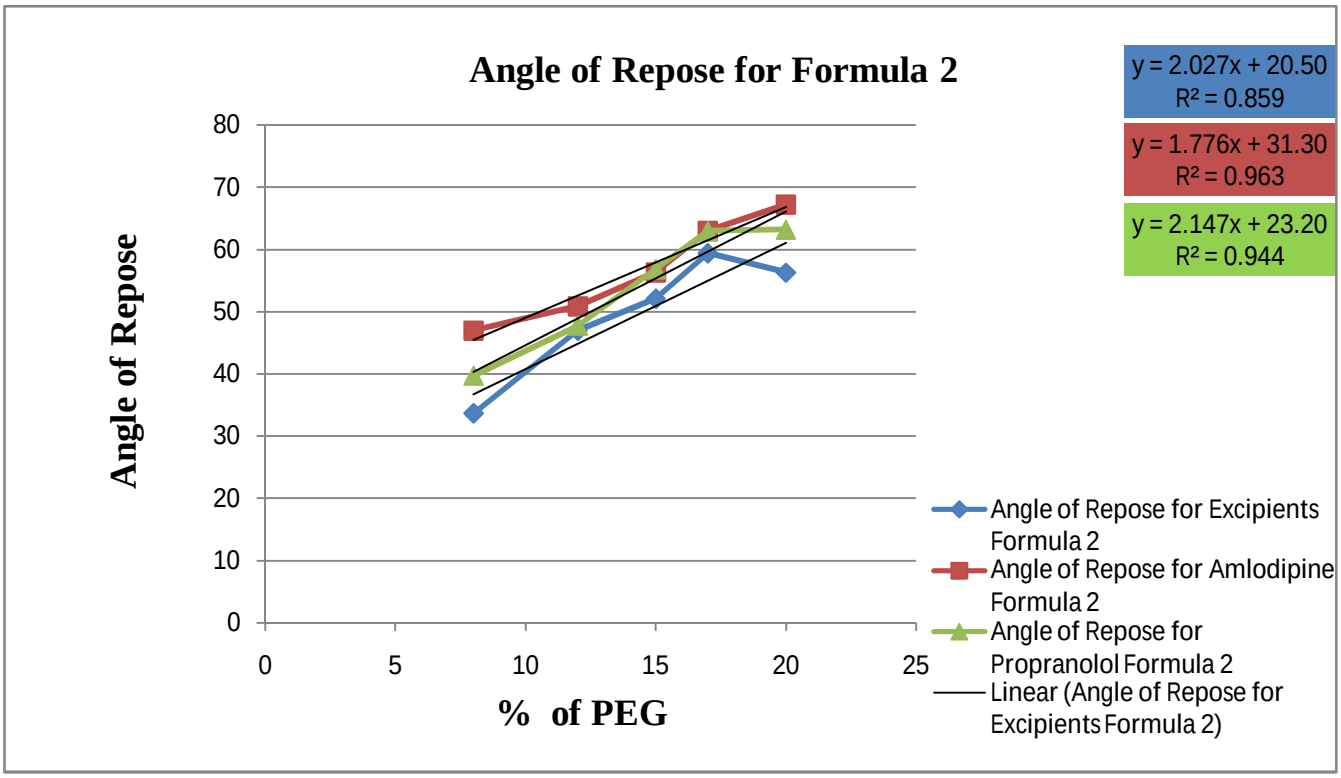

Figure 4.2(c): A percentage ratio of PEG versus Angle of repose graph (Formula 2)

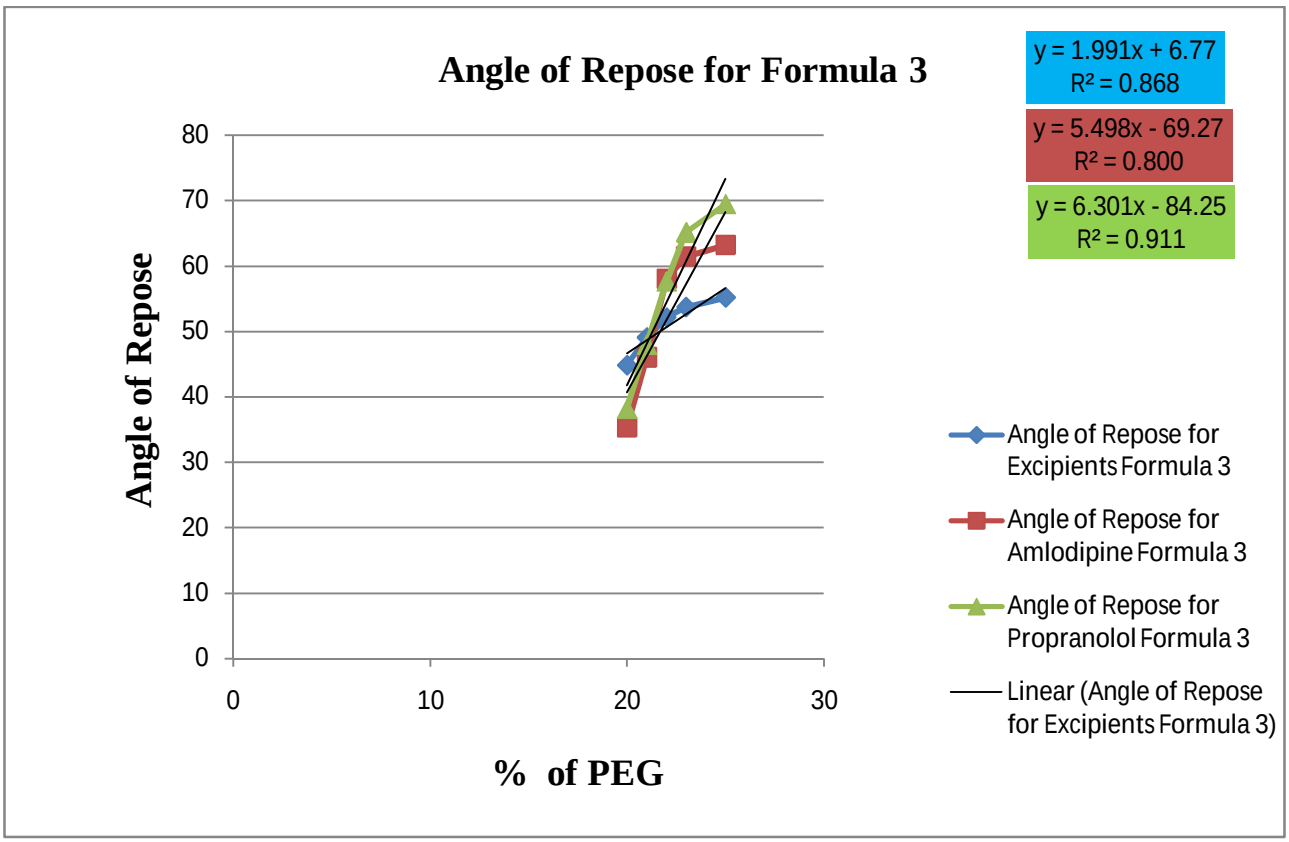

Figure 4.3(c): A percentage ratio of PEG versus Angle of repose graph (Formula 3)

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In this experiment, it was found that isolation of several equations of some pharmaceutical binders which helps to determine the flow property of the powder mixture. At what percentage the flow property will be maximum can be determined by those equations.

Table-5.1: Carr's Index Equations and Regression Value

Formulas(Sets)	Equation and Regression value
Excipients Formula- 1	$y = 3.275x + 0.019$ $R^2 = 0.887$
Excipients Formula 2	$y = 1.686x + 37.38$ $R^2 = 0.990$
Excipients Formula 3	$y = 3.392x – 55.05$ $R^2 = 0.907$
Amlodipine Formula 1	$y = 3.196x + 1.861$ $R^2 = 0.912$
Amlodipine Formula 2	$y = 1.420x + 9.575$ $R^2 = 0.908$
Amlodipine Formula 3	$y = 4.046x – 61.02$ $R^2 = 0.882$
Propranolol Formula 1	$y = 3.011x – 2.393$ $R^2 = 0.952$
Propranolol Formula 2	$y = 1.193x – 0.539$ $R^2 = 0.973$
Propranolol Formula 3	$y = 5.026x – 81.30$ $R^2 = 0.934$

Here, 'y' denotes Carr's Index and 'x' denotes the percentage of PEG. According to Carr's index Chart, flow of a powder mixture can be described. From the result of this work we see Decreased amount of PEG improved flow property of powder mixture.

Table-5.2: Hausner Ratio Equations and Regression Value

Formulas	Equation and Regression value
Excipients formula 1	$y = 0.102x + 0.448$ $R^2 = 0.950$
Excipients formula 2	$y = 0.027x + 0.876$ $R^2 = 0.876$
Excipients formula 3	$y = -0.011x + 1.554$ $R^2 = 0.967$
Amlodipine formula 1	$y = 0.093x + 0.571$ $R^2 = 0.908$
Amlodipine formula 2	$y = 0.025x + 0.830$ $R^2 = 0.979$
Amlodipine formula 3	$y = 0.027x + 0.876$ $R^2 = 0.820$
Propranolol formula 1	$y = 0.073x + 0.624$ $R^2 = 0.921$
Propranolol formula 2	$y = 0.027x + 1.053$ $R^2 = 0.943$
Propranolol formula 3	$y = 0.027x + 1.053$ $R^2 = 0.943$

Here, 'y' denotes Hausners ratio and 'x' denotes the percentage of PEG. According to Hausner's ratio, flow of a powder mixture can be described. From the result of this work we see decreased amount of PEG improved flow property of powder mixture.

Table-5.3: Angle of Repose Equations and Regression Value

Formulas	Equation and Regression value
Excipients formula 1	$y = 3.251x + 5.608$ $R^2 = 0.869$
Excipients formula 2	$y = 2.027x + 20.50$ $R^2 = 0.859$
Excipients formula 3	$y = 1.991x + 6.77$ $R^2 = 0.868$
Amlodipine formula 1	$y = 3.275x + 11.59$ $R^2 = 0.976$
Amlodipine formula 2	$y = 1.771x + 31.40$ $R^2 = 0.958$
Amlodipine formula 3	$y = 5.498x - 69.27$ $R^2 = 0.800$
Propranolol formula 1	$y = 4.371x + 6.619$ $R^2 = 0.932$
Propranolol formula 2	$y = 2.409x + 20.21$ $R^2 = 0.986$
Propranolol formula 3	$y = 6.302x – 84.25$ $R^2 = 0.910$

Here, 'y' denotes Angle of Repose and 'x' denotes the percentage of PEG. From the result of this work we see decreased amount of PEG improved flow property of powder mixture.

Chapter five

Discussions

5.1 Discussion

This work was proposed to determine the variation of flow properties of different Formulas of PVP along with Amlodipine and Propranolol. Different parameters to determine flow property such as Compressibility index, Hausner ratio, and angle of repose were observed. Individual flow property of the excipients was also determined. PVP was mixed with these prepared formulas in different specific and justified ratio. The prepared mixture in a constant weight was then examined for measuring flow property. The study showed a bit range of deviation of flow property between different ratios of mixture. The values of Carr's index, Hausner ratio and angle of repose were plotted against the percentage ratios of PVP. 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.

- In case of **SET-1,** the calculated value (Table 4.1, 4.2) and graph (Figure 4.1(a), 4.1(b), 4.1(c)) signified that, the mixture of ratio of PEG showed that the Carr's index, Hausner ratio and angle of repose gradually increased with the increasing ratio of PEG in that mixture of formula. It was stated above that the lower the value of Carr's index, Hausner ratio and angle of repose, the better the flow property. So for this set, the most desirable flow was obtained when the ratio of PEG and formula-1 is 10%:90%.From table 4.3, it can also be said that the values of Carr's index and Hausner ratio lied in between the good range (Table 4.1). The measured value of angle of repose (Table 4.2) for 10%:90% (PEG: F1) also lied in between the good range also.

- After then Amlodipine and Propranolol (In case of **SET-4, SET-7**) was mixed with the Formula 1 and flow property was measured using Carr's Index, Hausner ratio and angle of repose (Table 4.7, 4.8, 4.13, 4.14)The values of Carr's Index, Hausner ratio and angle of repose was in between good to passable range. After that the comparison between these two, a graph was built. (Figure 4.1(a), 4.1(b), 4.1(c)) and it can be said that, by increasing the amount of PEG, the flow property gradually decreased.

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- In case of **SET-2,** the calculated value (Table 4.3, 4.4) and graph (Figure 4.2(a), 4.2(b), 4.2(c) signified that, the most desirable flow property was observed in the ratio of 8%:92% (PEG: F2) when Carr's index and Hausner ratio were calculated. From Table 4.3, the flowability decreases with the increasing quantity of PEG added. So in these case, 8%:92% (PEG: F2) ratio showed best flow property (Figure 4.2(a), 4.2(b), 4.2(c)) than the other one. From table 4.3, it can also be said that for the ratio of 15%:75%,17%:83%, 20%:80% the value of Carr's index lied in between the poor range and the value of Hausner ratio also lied in between the poor or very poor range (Table 4.3). The measured value of angle of repose (Table 4.4) for 8%:92% (PEG: F2) lied in between the good range.
- After then Amlodipine and Propranolol (In case of **SET-5, SET-8**) was mixed with the Formula 2 and flow property was measured using Carr's Index, Hausner ratio and angle of repose (Table 4.9, 4.10, 4.15, 4.16)The values of Carr's Index, Hausner ratio and angle of repose was in between good to fair range. After that the comparison between these two, a graph was built. (Figure 4.2(a), 4.2(b), 4.2(c)) and it can be said that, by increasing the amount of PEG, the flow property gradually decreased. we can also say that the ratio 8%:92% (PEG:F2) showed the best flow property.

- In case of **SET-3**, the calculated value (Table 4.5, 4.6) and graph (Figure 4.3(a), 4.3(b) and 4.3(c)) signified that, the mixture of ratio having high quantity of PEG showed passable to poor flow property than the other ratios as the values of the Carr's index and Hausner ratio gradually increased with the increasing ratio of PEG in that mixture of formula. In these case, 20%:80% ratio (PEG: F3) showed better flowability and the values lied in between the fair range. The angle of repose was (Table 4.6, Figure 4.3(c)) within the very poor range of flow property.
- After then Amlodipine and Propranolol (In case of **SET-6, SET-9**) was mixed with the Formula 3 and flow property was measured using Carr's Index, Hausner ratio and angle of repose (Table 4.11, 4.12, 4.17, 4.18)The values of Carr's Index, Hausner ratio and angle of repose was in between poor to very poor range. After that the comparison between these two, a graph was built. (Figure 4.3(a), 4.3(b), 4.3(c)) and it can be said that, by increasing the amount of PEG, the flow property gradually decreased.

Chapter six

ConClusion

Determination of variation in Flow Property of Different Formulas of PEG (Polyethylene Glycol) along with Amlodipine and Propranolol

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 excipients are used as a major portion of a solid dosage form, its flow property is of particular interest. This experiment was done to isolate several equations of some pharmaceutical binders. These equations will help the future researchers and pharmaceutical personnel to predict and determine the flowability of mixtures for adding the above mentioned binders (PEG). Moreover, the plotted graphs and the equations for each set of formula were obtained which can be used to predict the flow property of these formulas with different ratio of diluents. This would help any future query about the flow property of any set of excipients in different ratios.

Chapter seven

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