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

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

DECLARATION BY THE RESEARCH CANDIDATE

I, Md. Zahid Ud Zaman, hereby declare that the dissertation, entitled "DETERMINATION OF VARIATION IN FLOW PROPERTY OF DIFFERENT SET OF FORMULAS OF LACTOSE ALONG WITH AMLODIPINE AND PROPRANOLOL" submitted by me to the Department of Pharmacy, East West University is an authentic and genuine thesis project carried out by me under the supervision and guidance of Mr. Mohammed Faisal Bin Karim, Senior Lecturer, Department of Pharmacy, East West University, Dhaka.

Signature of the candidate

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CERTIFICATE BY THE SUPERVISOR

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

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ENDORSEMENT BY HEAD OF THE DEPARTMENT

This is to certify that the dissertation entitled "DETERMINATION OF VARIATION IN FLOW PROPERTY OF DIFFERENT SET OF FORMULAS OF LACTOSE ALONG WITH AMLODIPINE AND PROPRANOLOL" submitted by Md. Zahid Ud Zaman is a genuine research work under the supervision of Mr. Mohammed Faisal Bin Karim(Senior Lecturer, Department of Pharmacy, East West University, Dhaka). I further certify that no part of the thesis has been submitted for any other degree and all the resources of the information in this connection are duly acknowledged.

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Dedication

This Research Paper Is Dedicated

To

My Beloved Parents

ABSTRACT

This work was proposed to determine the flow properties of different set of pharmaceutical excipients formulations that are used in directlycompressible tablets and to search for some equations which can predict the flow property of the excipients with different ratio of diluents. Here we determine the flow property of formulation with amlodipine and propranolol and compare with excipient formulation. Compressibility index, Hausner ratio, and angle of repose were used as parameters of determining flow properties. Diluents were mixed with these prepared formulas in different specific and justified ratio. The prepared mixture in a constant weight was then examined for measuring flow property with and without APIs. The values of Carr's index, Hausner ratio and angle of repose were plotted against the percentage ratios of diluents. The study showed a linear relationship with different ratios of mixture and flow property measuring parameters. From the graphs the straight line equation for each set of formula were obtained regression value which can be used to predict the flow property of the formula with different ratio of diluents. Moreover the most suitable ratio of specific diluents and a specific set of other excipients were proposed that showed better flow property with amlodipine and propranolol. After doing research I found that the best result comes from set-1 is ratio 5 (85% : 15%), for set-2 is ratio 5 (70% : 30%) and for set-3 is ratio 4 (85% : 15%). And bad result comes from set-1 is ratio 1 (45% : 55%), for set-2 is ratio 1 (30% : 70%) and also for set-3 is ratio 1 (55% : 45%). These equations can be used for other APIs also to determine their flow property.

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

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Introduction

1.1 Introduction

The objective of this research is to evaluate that ratio of pharmaceutical excipients in a mixture that will provide maximum flow property. We are focusing to isolate a specific equation which will explain the flowability of a formulation. 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(Young, 2015).

1.2 Powder Flow

The widespread use of powders in the pharmaceutical industry has created a variety of methods for symbolizing powder flow (USP29-NF24, 2013). Not surprisingly, scores of references appear in the pharmaceutical literature, trying to relate the various measures of powder flow to manufacturing properties. The development of such a variety of test methods was unavoidable and the behaviors of powder flow properties are many-sided and this complicates the effort to characterize the powder flow. The reason of this part is to review the methods for characterizing powder flow. No single and simple test method can adequately characterize the flow properties of pharmaceutical powders; this part proposes the standardization of test methods that may be valuable during pharmaceutical development(Hart, 2015). Four commonly described methods for testing powder flow are-

(1) Angle of repose,

(2) Compressibility index or Carr's Index,

(3) Hausner's ratio, and

(4) Shear cell.

In addition numerous variations of each of these basic methods are available.

1.2.1 Flow Properties Tests (Durst, 2008)

Key bulk material flow properties that should be measured for troubleshooting problems, assessing powder flowability, or designing a bulk material handling system are:

- **Cohesive strength:** powder flowability through hoppers
- **Wall friction:** hopper angles to achieve mass flow
- **Internal friction:** static and kinematic angles of internal friction
- **Compressibility:** bulk density as a function of major consolidating pressure
- **Permeability:** gas/solids interactions; limiting discharge rates from hoppers
- **Angle of repose:** angle of pile of material at rest
- **Loose/tap density:** bulk density measured before and after vibration
- **Chute:** chute angles required to maintain flow after impact

1.2.2 Importance of flow property (Durst, 2008)

A thorough understanding of a bulk material's flow properties and its flowability are crucial for identifying the cause of poor flow, powder flooding or rate limitations, segregation, or product non-uniformity. Flow properties tests are also critical when designing a new silo/bin/hopper, stockpile, feeder, chute, conveyor or other material handling equipment. Issues can arise or be compounded when powder and bulk solids flow properties have not been measured, the test results may be limited, or the data are non-representative of the application.

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

6. By observing flow property of pharmaceutical excipients some physical properties of desired pharmaceutical product such as weight uniformity, content uniformity, hardness, disintegration time can be maintained.

7. To design reliable devices for the handling of bulk solids, knowledge of the flow properties of these bulk solids is essential.

1.2.3 Factors influencing flow property

Factors that have impact or influence on flow property are as follows

a. Particle size: Particle size play significant roles in flow property. Reduction in particle size often tends to decrease the flowability of a given granular material due to the increased surface area per unit mass. (Fitzpatricket al., 2004)

b. 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 pestle to provide uniform properties. (Johanson, 1978)

c. Temperature: Temperature also has a substantial effect on bulk solid flow-ability. The most drastic temperature effect is the freezing of the moisture contained within the granular materials and on particle surfaces. The resulting ice bonds weaken the flow (Irani et al., 1959; Johanson, 1978; Fitzpatrick et al., 2004).

d. Pressure: Compacting pressure is also an important factor that affects the flow properties of bulk solids. The bulk may be subjected to compaction due to vibration (e.g., during trans-portation), impact from a falling stream of solids (e.g., during silo filling), or external loading. The effect of increased pres-sure on flowability of powders is twofold: (1) it leads to a larger number of contact points between particles, thus causing more inter-particle adhesion (Irani et al., 1959); and (2) the increased compaction

produces a significant increase in critical arching dimensions (Johanson, 1978).

e. Fat content: Free surface fat is expected to play a key role in granular flowability as well, but has not been extensively researched to date. For example, high fat content (20%) spray dried soymilk led to worse flow of the resulting soymilk powders (Perez and Flores., 1997). Further, free fat content, varying from 13 to 74%, had no major impact on the cohesion of a 26% fat milk powder at 20%C (Fitzpatrick et al., 2004).

f. Flow conditioners and anticaking agents: Caking and stickiness are common problems that almost every industry dealing with granular solids and powders encounters. Caking is defined as when two or more macro-particles, each capable of independent translational movement, contact and interact to form a congregate in which the particles are incapable of independent translations (Barbosa et al., 2003). Flow conditioners and anticaking agents are commonly used as additives that can assist a powder in maintaining a steady flow and/or increase its flow rate. Flow conditioners are usually made from chemically inert substances and are often effective at concentrations up to 2%. Most are insoluble in water, but many of them can adsorb significant quantities of moisture as a result of their very large surface areas. (Barbosa et al., 2003)

1.3 Angle of repose

The angle of repose or the critical angle of repose, of a granular material is the steepest angle of descent or dip relative to the horizontal plane to which a material can be piled without slumping. At this angle, the material on the slope face is on the verge of sliding.

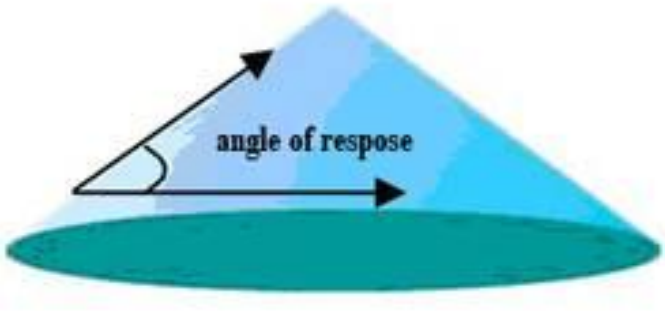


Figure 1.1: Angle of repose (Merriam, 2013)

Angle of repose is defined as the angle between the horizontal and the slope of a heap of granular material dropped from some designated elevation. Angle of repose corresponds qualitatively to the flow properties of that material, and is a direct indication of potential flowability. Angle of repose of a bulk solid can be described using the following equation (Fowler and Wyatt, 1960; Mohsenin, 1986; Rao, 1992):

$$\tan\Phi_r = an^2 + b\frac{M}{D_{av}} + cs_g + d$$

Where Fr is angle of repose (degrees); n is shape factor based on specific surface (–);M is moisture content (db %); D_{av} is average particle diameter (cm);S_g is specific gravity (–);a, b, c, and d are empirical constants. Most often, however, angle of repose is determined experimentally by allowing a sample to flow onto a flat surface, and then measuring the angle with respect to horizontal. There is much literature available on the angle of repose of granular materials (like food, grains, industrial powders, pharmaceutical powders, etc.) but not on DDGS. Typically, the lower the angle of repose of a dry material, the more flowable the material is, and vice versa (Carr, 1965a). Higher angles (i.e., 50–60%) indicate material with difficult flow, while a lower angle, such as 30–40%), represents a material with relatively easy flow. Angle of repose gives a reproducible numerical value, so it has been adopted as a common method to assess flow properties (Craik and Miller, 1958). Generally the magnitude of angle of repose increases with increase in moisture content.

Table 1.1: Relation between flow properties and angle of repose (Pharmacopeia.cn, 2015)

Flow Properties	Angle of repose (^{0})
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Very very poor	>66

There are several methods for determining angle of repose (US Pharmacopoeia 29-NF24).
These are given below

a. **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 .3 degrees/second. Tilting is stopped when the material begins to slide in bulk, and the angle of the tilt is measured.

b. **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.

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

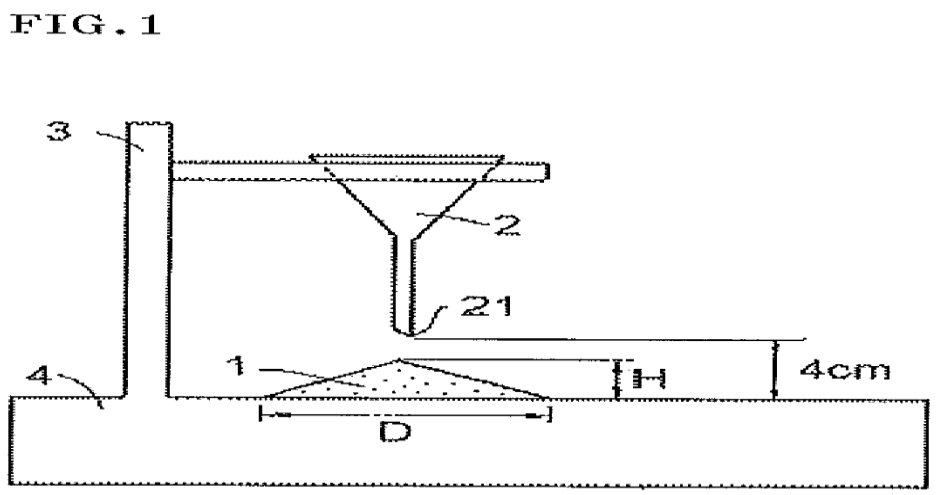


Figure 1.2: A set up of funnel with stand and measuring angle of repose

(US20120225974 A1, 2012)

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

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

(Merriam, 2013)

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

Factors that have impact or influence on angle of repose are as follows (Friedman and Robinson, 2002).

Shear strength of particles determines their angles of repose. Factors affecting shear strength include:

a. Properties of particles: Size and Angularity
b. Water content
c. Particle Size and Angularity: Greater angularity of particles will result in more inter-granular friction and interlocking of particles, contributing to greater shear strength and angle of repose. Particles with greater angularity interlock better with each other, resulting in higher intergranular friction. Particles that are rounder interlock less tightly, resulting in less intergranular friction. Spherical particles such as marbles do not interlock and therefore have extremely low intergranular friction.
d. Water Content and Cohesion Water content affects the cohesiveness of particles. If water is added to particles such as sand, water coating the grains would tend to bind them together by its surface tension, giving rise to greater internal cohesion, and therefore shear strength. However, if water is added to completely saturate the pore spaces, the pore water would act as a lubricant between grains and the pore pressure would force the grains apart. Particles interlock with each other. Angle of repose is smaller than when the sand is wet. Wet powders — grains covered with a layer of water. Water tension would increase the cohesiveness of the grains, resulting in higher shear strength and angle of repose. Powders saturated with water lubrication by water encourages down slope movement of particles. Water pressure in the pores would make the particles buoyant, reducing its shear strength and angle of repose.

1.4 Compressibility index and Hausner ratio

1.4.1 Compressibility Index

Carr's index also known as Carr's Compressibility Index. Much attention has been given to the behaviour of bulk solids under compressive stress. Typically, a set of compression cells is used to obtain the pressure–density relationship for a given material; the test material is compressed using a compression testing machine, and the force-deformation data must then be converted to a pressure–density relation (Hollenbach, et al., 1983; Barbosa-Canovas, et al., 1987; Barbosa-Canovas and Yan, 2003). A number of authors have suggested empirical equa-tions to describe these relationships. Three commonly used models are: Heckel, Kawakita and Ludde, and Sone (Malave et al., 1985; Barbosa and Yan, 2003). There are other ways to examine compressibility, however. Hausner ratio, the ratio between tapped and loose bulk density, is also used to quantify the compressibility of bulk solids. The compressibility of a material can also be computed by the following equation:

$$C=100(P-A)\backslash P$$

Where C is compressibility (%), P is packed bulk density, A is aerated bulk density (kg).

The greater the compressibility of a bulk solid, the less flowable it is. In general, the borderline between free flowing and non free flowing is approximately 20–21% compressibility (Carr, 1965). Compressibility and bulk density are related, and have been correlated using the following empirical equation (Peleg and Mannheim, 1973; Peleg, 1977; Hollenbachet al., 1983; Malaveet al., 1985):

$$BD = (a+b)\log P$$

Where, BD is bulk density (kg cm^{-3}); a is extrapolated BD at 1 $kgcm^{-2}$ pressure (kg cm^{-3});b is the slope of the straight line(compressibility) (kg cm^{-3}); P is applied pressure (kg cm^{-2}). A decrease in compressibility has been observed with an increase in the particle size (Yan and Barbosa-Canovas, 1997). A decrease in compressibility of various powders and granular solids was observed when conditioners were added (Peleg and Mannheim, 1973; Hollenbachet al., 1983).

DDGS is expected to gain moisture when exposed to higher humid conditions. This might increase the compressibility of DDGS and lead to flow problems.

The Carr's index is calculated by the formula below

$$C = 100\frac{V_B - V_T}{V_B}$$

(Slideshare, 2012)

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

1.4.2 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. 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 (Pharmacopeia.cn, 2015)

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}.$$

(Slideshare, 2012)

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

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

H=100/ (100-C)

Table 1.2: Relation between flow properties with Compressibility index (Carr's index) and Hausner ratio (Pharmacopeia.cn, 2015)

Flow property	AR(^{0})	CI(%)	HR
Excellent	25-30	≤10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.45-1.59
Very very poor	>66	>38	>1.60

Where, AR is Angle of repose, CI is The Carr's index an HR is Hausner ratio.

1.5 Bulk density and Tapped density (WHO, 2015)

1.5.1 Bulk density (WHO, 2015)

The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the interparticulate void volume. Hence, the bulk density depends on both the density of powder particles and the spatial arrangement of particles in the powder bed. The bulk density is expressed in grams per millilitre (g/ml) although the international unit is kilogram per cubic metre (1 g/ml = 1000 kg/m^3) because the measurements are made using cylinders.

It may also be expressed in grams per cubic centimetre (g/cm^3)

The bulking properties of a powder are dependent upon the preparation, treatment and storage of the sample, i.e. how it was handled. The particles can be packed to have a ra nge 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. The bulk density of a powder is determined by measuring the volume of a known mass of powder sample, that may have been passed through a sieve, into a graduated cylinder (Method

A), or by measuring the mass of a known volume of powder that has been passed through a volumeter into a cup (Method B) or a measuring vessel (Method C).

1.5.1.1 Method 1: Measurement in a Graduated Cylinder

Procedure:

Pass a quantity of powder sufficient to complete the test through a sieve with apertures greater than or equal to 1.0 mm, if necessary, to break up agglomerates that may have formed during storage; this must be done gently to avoid changing the nature of the material. Into a dry graduated cylinder of 250 mL (readable to 2 mL), gently introduce, without compacting, approximately 100 g of the test sample (m) weighed with 0.1 per cent accuracy. Carefully level the powder without compacting, if necessary, and read the unsettled apparent volume (V0) to the nearest graduated unit. Calculate the bulk density in g per mL by the formula m/V0. Generally, replicate determinations are desirable for the determination of this property. If the powder density is too low or too high, such that the test sample has an untapped apparent volume of either more than 250 mL or less than 150 mL, it is not possible to use 100 g of powder sample. Therefore, a different amount of powder has to be selected as test sample, such that its untapped apparent volume is 150 mL to 250 mL (apparent volume greater than or equal to 60 per cent of the total volume of the cylinder); the mass of the test sample is specified in the expression of results.For test samples having an apparent volume between 50 mL and 100 mL a 100 mL cylinder readable to 1 mL can be used; the volume of the cylinder is specified in the expression of results.

1.5.1.2 Method 2: Measurement in a Volumeter

Apparatus:

The apparatus (1) (Fig. 1.3) consists of a top funnel fitted with a 1.0 mm sieve. The funnel is mounted over a baffle box containing four glass baffle plates over which the powder slides and bounces as it passes. At the bottom of the baffle box is a funnel that collects the powder and allows it to pour into a cup mounted directly below it. The cup may be cylindrical (25.00 ±0.05 mL volume with an inside diameter of 30.00 ± 2.00 mm) or a cubical (16.39 ± 0.20 mL volume with inside dimensions of 25.4± 0.076 mm).

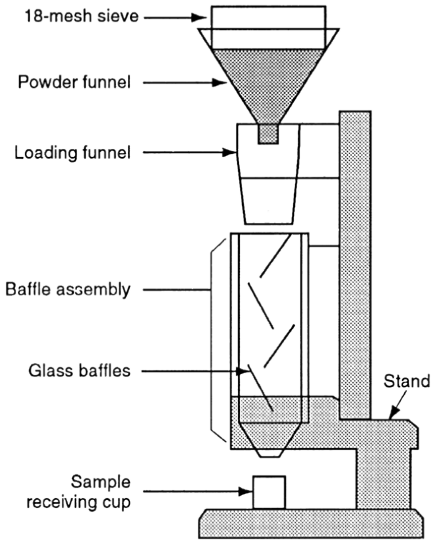


Figure 1.3: Volumeter (Scott Volumeter) (USP31- 2010)

Procedure:

Allow an excess of powder to flow through the apparatus into the sample receiving cup until it overflows, using a minimum of 25 $cm^3$of powder with the cubical cup and 35 $cm^3$of powder with the cylindrical cup. Carefully, scrape excess powder from the top of the cup by smoothly moving the edge of the blade of spatula perpendicular to and in contact with the top surface of the cup, taking care to keep the spatula perpendicular to prevent packing or removal of powder from the cup. Remove any material from the side of the cup and determine the mass (m) of the powder to the nearest 0.1 per cent. Calculate the bulk density in g per mL by the formula m/V_0 in which V_0 is the volume of the cup and record the average of 3 determinations using 3 different powder samples.

1.5.1.3 Method 3: Measurement in a Vessel

Apparatus:

The apparatus consists of a 100 mL cylindrical vessel of stainless steel with dimensions as specified in Fig. 1.4

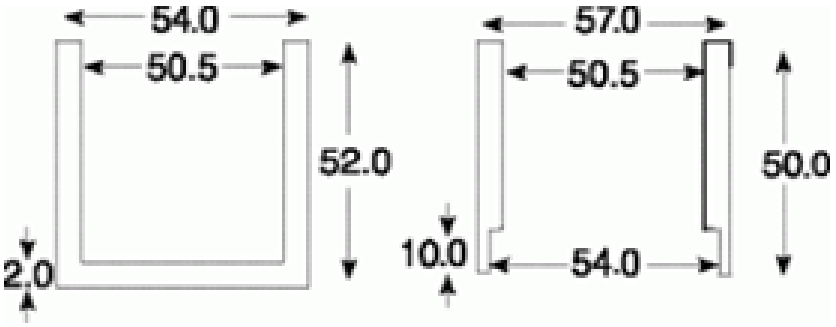


Figure 1.4: Measuring vessel (left) and cap (right) Dimensions in mm

(WHO, 2015)

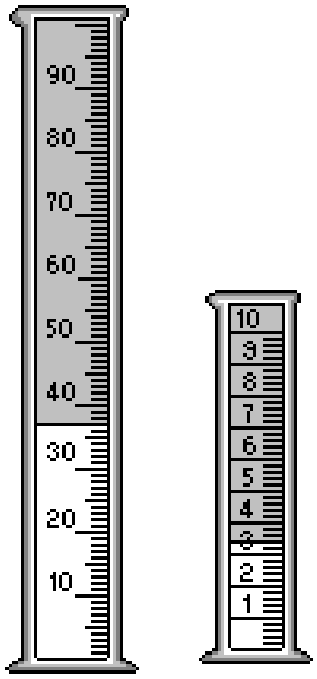
Procedure:

Pass a quantity of powder sufficient to complete the test through a 1.0 mm sieve, if necessary , to break up agglomerates that may have formed during storage and allow the obtained sample to flow freely into the measuring vessel until it overflows. Carefully scrape the excess powder from the top of the vessel as described for Method 2. Determine the mass (m0) of the powder to the nearest 0.1 per cent by subtraction of the previously determined mass of the empty measuring vessel. Calculate the bulk density (g/mL) by the formula m0/100 and record the average of 3 determinations using 3 different powder samples.

1.5.2 Tapped density (WHO, 2015)

The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample.

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.



A B

Figure 1.5: Bulk volume measurement without tapping (A) and Tapped volume measurement after tapping (B) (Alanpedia, 2015)

1.5.3 Factors that influence the tapped density (International Pharmacopoeia, 2015)

a. The mass of the material
b. Rotation of the sample
c. The diameter of the cylinder
d. The number of times the powder is tapped

1.5.4 Methods of determining tapped density (WHO, 2015)

1.5.4.1 Method 1

Apparatus

The apparatus (Fig. 3.01-3) consists of the following:– a 250 mL graduated cylinder (readable to 2 mL) with a mass of 220 ± 44 g.– a settling apparatus capable of producing, in 1 min, either nominally 250 ± 15 taps from a height of 3 ± 0.2 mm, or nominally 300 ± 15 taps from a

height of 14 ± 2 mm. The support for the graduated cylinder, with its holder, has a mass of 450 ± 10 g.

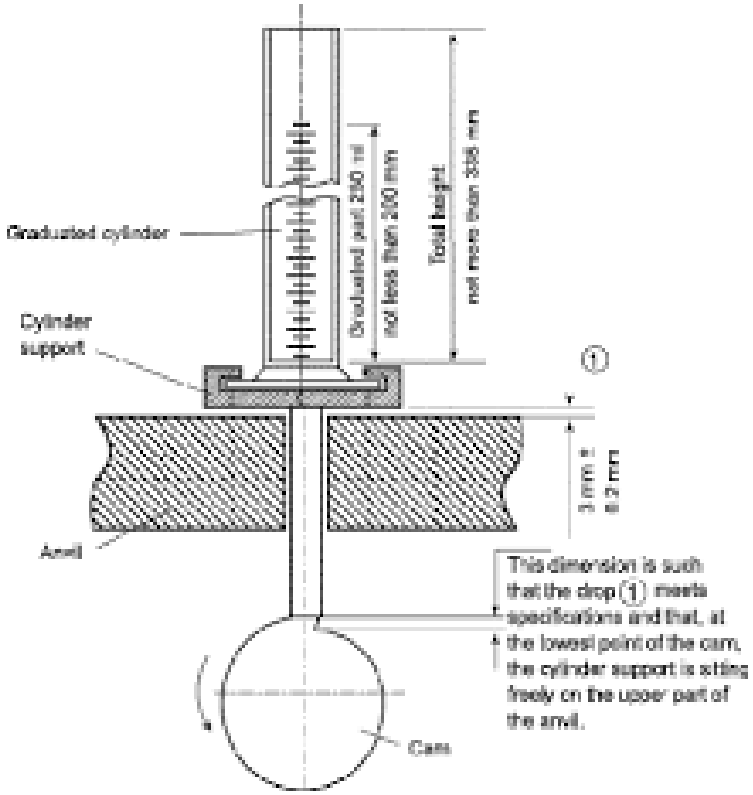


Figure 1.6: Tapped density tester

(WHO, 2015)

Procedure

Proceed as described above for the determination of the bulk volume (V_0). Secure the cylinder in the holder. Carry out 10, 500 and 1250 taps on the same powder sample and read the corresponding volumes V_{10}, V_{500} and V_{1250} to the nearest graduated unit. If the difference between V_{500} and $V^{1250}$is less than or equal to 2 mL, $V_{1250}$is the tapped volume. If the difference between $V_{500}$and V_{1250} exceeds 2 mL, repeat in increments such as 1250 taps, until the difference between succeeding measurements is less than or equal to 2 mL. Fewer taps may be appropriate for some powders, when validated. Calculate the tapped density (g/mL) using the formula m/V_f in which V_f is the final tapped volume. Generally, replicate determinations are desirable for the determination of this property. Specify the drop height with the results. If it is not possible to use

a 100 g test sample, use a reduced amount and a suitable 100 mL graduated cylinder (readable to 1 mL) weighing 130 ± 16 g and mounted on a holder weighing 240 ± 12 g. The modified test conditions are specified in the expression of the results.

1.5.4.2 Method 2

Procedure

Proceed as directed under Method 1 except that the mechanical tester provides a fixed drop of 3 ± 0.2 mm at a nominal rate of 250 taps per minute.

1.5.4.3 Method 3

Procedure

Proceed as described in the method for measuring the bulk density using the measuring vessel equipped with the cap shown in Fig. 1.4. The measuring vessel with the cap is lifted 50-60 times per minute by the use of a suitable tapped density tester. Carry out 200 taps, remove the cap and carefully scrape excess powder from the top of the measuring vessel as described in Method 3 for measuring the bulk density. Repeat the procedure using 400 taps. If the difference between the 2 masses obtained after 200 and 400 taps exceeds 2 per cent, carry out a test using 200 additional taps until the difference between succeeding measurements is less than 2 per cent. Calculate the tapped density (g/mL) using the formula mf/100 where mfis the mass of powder in the measuring vessel. Record the average of 3 determinations using 3 different powder samples. The test conditions including tapping height are specified in the expression of the results.

1.6 Excipient

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 (USP-NF V3.1, 2007).

1.6.1 Some common excipients used in pharmaceutical formulation and their function

Excipients play a crucial role in design of the delivery system, determining its quality and performance. Excipients though usually regarded as nontoxic there are examples of known excipient induced toxicities which include renal failure and death from diethylene glycol, osmotic diarrhoea caused by ingested mannitol, hypersensitivity reactions from lanolin and cardiotoxicity induced by propylene glycol (USP29-NF24, 2013).

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

1.6.1.1 Types (Haywood and Glass, 2011):

- Fillers
- Binders
- Disintegrants
- Coatings
- Sorbents
- Antiadherent
- Lubricants
- Glidants
- Preservatives
- Antioxidants
- Flavoring Agents
- Sweeting Agents

- Coloring Agents
- Solvent & Co-solvent
- Buffering Agents
- Chelating Agents
- Viscosity imparting Agents
- Surface Active Agents
- Humectants

1.6.2 Function of pharmaceutical excipients of various classes

1.6.2.1 Fillers (Patel, Shah and Upadhyay, 2015)**:**

Fillers typically also fill out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use.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.

- Typical features of fillers: A good filler should typically be inert, compatible with the other components of the formulation, non-hygroscopic, relatively cheap, compactible, and preferably tasteless or pleasant tasting.

- Examples: Plant cellulose and dibasic calcium phosphate are used popularly as fillers . A range of vegetable fats and oils can be used in soft gelatin capsules. Other examples of fillers include: lactose, sucrose, glucose, mannitol, sorbitol, calcium carbonate, and magnesium stearate.

1.6.2.2 Binders (Mattsson, 2013)

Binders hold the ingredients in a tablet together. Binders ensure that tablets and granules can be formed with required mechanical strength, and give volume to low active dose tablets. Binders act as an adhesive to 'bind together' powders, granules and tablets to result in the necessary mechanical strength. Binders are added to tablet formulations to add cohesiveness to powders thereby providing the necessary bonding to form granules which under compaction form a compact mass as tablet. In other words, binders are essential to achieve the "hardness" of the

tablet.Tablet binders are used in the formulation of solid oral dosage forms to hold the active pharmaceutical ingredient and inactive ingredients together in a cohesive mix. Binder products are usually differentiated based on the manufacturing process to be used. Binders are usually selected on basis of previous experience, particular product needs, literature or vendor data or the preference of individual scientists or manufacturing unit. The primary criterion when choosing a binder is its compatibility with other tablet components (Drugtopics, 2008).

Typical features of binders

A binder should be compatible with other products of formulation and add sufficient cohesion to the powders .

Classification and examples

Binders are classified according to their application,

- Solution binders are dissolved in a solvent (for example water or alcohol can be used in wet granulation processes). Examples include gelatin, cellulose, cellulose derivatives, polyvinylpyrrolidone, Lactose, sucrose and polyethylene glycol.

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

1.6.2.3 Disintigrants (Gohel, 2015)

Disintegrants are substances or mixture of substances added to the drug formulations, which facilitate dispersion or breakup of tablets and contents of capsules into smaller particles for quick dissolution when it comes in contact with water in the GIT. It can also be used with products that are wet granulated. While there are some tablet fillers (e.g., Lactose and microcrystalline cellulose) which aid in disintegration, there are more effective agents referred to as superdisintegrants. They ensure that when the tablet is in contact with water, it rapidly breaks down into smaller fragments, facilitating dissolution.

- Ideal properties: Good hydration capacity , poor solubility , poor gel formation capacity .
- Examples: polyvinyl pyrrolidone , carboxymethyl cellulose, sodium Lactose glycolate etc

1.6.2.4 Coating Agents (Felton and McGinity 2008)

Coating is a process by which an essentially dry, outer layer of coating material is applied to the surface of a dosage form and agents which are used in this coating process is called coating agents

Types:

Three types of coating agents are used pharmaceutically,

a. Film coating
b. Sugar coating
c. Compression coating

Function of coating agents:

- Protection
- maskin elegance
- ease of swallowing
- identification etc.

Examples:

HPMC, MC, HPC etc.

1.6.2.5 Sorbents (Possumato, 2007)

Sorbents are insoluble materials or mixtures of materials used to recover liquids through the mechanism of absorption, or adsorption, or both. *Ab*sorbents are materials that pick up and retain liquid causing the material to swell (50 percent or more).*Ad*sorbents are insoluble materials that are coated by a liquid on its surface. To be useful in combating oil spills, sorbents need to be both oleophilic (oil-attracting) and hydrophobic (water-repellent). Although they may be used as the sole cleanup method in small spills, sorbents are most often used to remove final traces of oil, or in areas that cannot be reached by skimmers. Sorbent materials and any oil that is removed from sorbent materials must be disposed of in accordance with approved local, state, and federal regulations.

Sorbents can be divided into three basic categories:

Natural organic sorbents include:

- peat moss,
- straw,
- hay,
- sawdust,
- ground corncobs,
- feathers, and
- other readily available carbon-based products.

Organic sorbents can adsorbs between 3 and 15 times their weight in oil, but there are disadvantages to their use. Some organic sorbents tend to adsorbs water as well as oil, causing the sorbents to sink. Many organic sorbents are loose particles and are difficult to collect after they are spread on the water. These problems can be counterbalanced by adding flotation devices. For example, empty drums attached to sorbent bales of hay overcome the sinking issue. Mesh can be wrapped around loose particles to aid in collection.

Natural inorganic sorbents consist of:

- clay,
- perlite,
- vermiculite,
- glass wool,
- sand, or
- volcanic ash.

They can adsorb from 4 to 20 times their weight in oil. Inorganic sorbents, like organic sorbents, are inexpensive and readily available in large quantities. These types of sorbents are not used on the water's surface.

Synthetic sorbents

They include man-made materials that are similar to plastics, such as polyurethane, polyethylene, and polypropylene. They are designed to adsorb liquids onto their surfaces. Other synthetic sorbents include cross-linked polymers and rubber materials, which absorb liquids into their solid structure, causing the sorbent material to swell. Most synthetic sorbents can absorb up 70 times their own weight in oil.

The characteristics of both sorbents and oil types must be considered when choosing sorbents for cleaning up oil spills:

- Rate of absorption -- The absorption of oil is faster with lighter oil products. Once absorbed the oil cannot be re-released. Effective with light hydrocarbons (e.g., gasoline, diesel fuel, benzene).
- Rate of adsorption -- The thicker oils adhere to the surface of the adsorbent more effectively.
- Oil retention -- The weight of recovered oil can cause a sorbent structure to sag and deform, and when it is lifted out of the water, it can release oil that is trapped in its pores. Lighter, less viscous oil is lost through the pores more easily than are heavier, more viscous oils during recovery of adsorbent materials causing secondary contamination.
- Ease of application -- Sorbents may be applied to spills manually or mechanically, using blowers or fans. Many natural organic sorbents that exist as loose materials, such as clay and vermiculite, are dusty, difficult to apply in windy conditions, and potentially hazardous if inhaled.

1.6.2.6 Antiadherents (Rowe C., et al., 2009)

Antiaderents or anti-sticking agents prevent adhesion of the tablet surface to the die walls and the punches and as a consequence counter the picking or sticking of tablet. They are also used to help protect tablets from sticking. Some materials have strong adhesive properties towards the metal ofpunches 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.

Examples:

Water insoluble lubricants such as magnesium stearate can be used as antiadherents , as can talc and Lactose.

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

These have excellent antiadherent properties.

1.6.2.7 Lubricants (Gohel, 2015)

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

Examples

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

Types:

- Hydrophilic- Generally poor lubricants, no glidant or anti-adherent properties.
- Hydrophobic-Most widely used lubricants in use today are of the hydrophobic category. Hydrophobic lubricants are generally good lubricants and are usually effective at relatively low concentrations. Many also have both anti- adherent and glidant properties. For these reasons, hydrophobic lubricants are used much more frequently than hydrophilic compounds. Examples include magnesium stearate.

Roles of lubricants:

a. True Lubricant Role:

- To decrease friction at the interface between a tablet's surface and the die wall during ejection and reduce wear on punches & dies.

b. Anti-adherent Role:

- Prevent sticking to punch faces or in the case of encapsulation, lubricants
- Prevent sticking to machine dosators, tamping pins, etc.

c. Glidant Role:

- Enhance product flow by reducing interparticulate friction

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

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

1.6.2.8 Glidants (Gohel, 2015)

A substance (as colloidal silica) that enhances the flow of a granular mixture by reducing inter-particle friction and that is used in the pharmaceutical production of tablets and capsule.

Functions of glidants:

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.

Examples:

- Fumed silica
- Talc
- magnesium carbonate.

1.6.2.9 Preservatives (Patel, Shah and Upadhyay, 2015)

Preservatives are substances that commonly added to various foods and pharmaceutical products in order to prolong their shelf life.

Ideal properties of preservatives:

In concept, the preservative system protects the product against microbial proliferation but does not compromise product performance. In practice, this means that it must:

- Exert a wide spectrum of antimicrobial activity at low inclusion levels.
- Maintain activity throughout product manufacture, shelf life and usage.
- Not compromise the quality or performance of product, pack or delivery system.
- Not adversely affect patient safety or tolerance of the product.

Examples:

- Methyl & Ethyl parabens
- Propyl paraben
- Benzoic acid and its salts
- Sorbic acid and its salts.

1.6.2.10 Antioxidant (Gohel, 2015)

An antioxidant is a molecule that inhibits the oxidation of other molecules. Oxidation is a chemical reaction that transfers electrons or hydrogen from a substance to an oxidizing agent.

Ideal Properties of Antioxidants:

- Effective at a low, nontoxic concentration
- Stable and effective under normal conditions of use, over a wide pH and temperature range
- Soluble at the required concentration
- Compatible with a wide variety of drugs and pharmaceutical excipients
- Free from objectionable odor, objectionable taste
- Colorless in both the original and oxidized form
- Nontoxic both internally and externally at the required concentration
- Reasonable cost

- Unreactive (does not adsorb, penetrate, or interact) with containers or closures

Examples:

- BHT(Butylated Hydroxy Toluene)
- BHA(Butylated Hydroxy Anisol)
- Sodium sulfite
- Ascorbic acid etc..

1.6.2.11 Sweetening agents (Patel, Shah and Upadhyay, 2015)

Sweetening agents are employed in liquid formulations designed for oral administration specifically to increase the palatability of the therapeutic agent.

Example:

- Sucrouse
- Saccarine
- Aspertame
- Sorbitol etc.

Uses of sweetening agent:

The main sweetening agents employed in oral preparations are sucrose, liquid glucose, glycerol, sorbitol, saccharin sodium and aspartame. Aspartame is an artificial sweetening agent. The use of artificial sweetening agents in formulations is increasing. The use of sugars in oral formulations for children and patients with diabetes mellitus is to be avoided.

1.6.2.12 Flavoring agents (Patel, Shah and Upadhyay, 2015)

Flavouring agents are added to increase patient acceptance. The four basic taste sensations are salty, sweet, bitter and sour. It has been proposed that certain flavours should be used to mask these specific taste sensations.

Example:

- Clove oil
- citric and syrup
- glycerin
- rose oil

- orange oil
- menthol etc.

1.6.2.13 Coloring agents (Gohel, 2015)

Coloring agents are pharmaceutical ingredients that impart the preferred color to the formulation.

There are two types of coloring agents

a. Natural and
b. synthetic

Example:

- White: Titanium dioxide
- Blue: Brilliant blue, Indigo carmine
- Red: Amaranth Carmine
- Yellow: saffron
- Green
- Brown: caramel

1.6.2.14 Solvents (Welton and Reichardt, 2010)

A solvent is a substance that can dissolve a solute (a chemically different liquid , solid or gas) resulting in solution. A solvent is usually a liquid but it can also be solid or a gas. A solvent never changes its state forming a solution.

Solvent classification

Solvents can be broadly classified into two groups; They are

- Polar
- Non polar

Normally solvation of a solvent depends upon its classification. Generally polar solvent dissolves polar compound best and non polar solvent dissolves non polar compound best.

Example and uses of solvent

- The first choice for a solvent is water in which a drug is freely soluble.
- Water –miscible solvent such as Chlordiazepoxide hydrochloride can be used to improve solubility and stability.
- Oils are used as emulsion, intramuscular injections and liquid fill oral preparation.
- Aqueous methanol is widely used in HPLC and is the standard solvent in sample extraction.
- Other acceptable non-aqueous solvents are glycerol ,propylene glycol, ethanol and are used generally for a lipophilic drug.

1.6.2.15 Co-solvents (Welton and Reichardt, 2010)

Co-solvents are defined as water-miscible organic solvents that are used in liquid drug formulations to increase the solubility of poorly water soluble substances or to enhance the chemical stability of a drug.

Properties of co-solvent

- Co-solvent increases the solubility of a drug.
- An ideal co-solvent should possess values of dielectric constant between 25 and 80.
- The most widely used system that will cover this range is a water/ethanol blend.
- It should not cause toxicity or irritancy when administrated for oral or parental use
- Other co-solvents are sorbitol, glycerol, propylene glycol and syrup.

1.6.2.16 Chelating agent (Goel and Gautam, 2012)

Chelating agents are molecules that are capable of forming complexes with the drug involving more than one bond it's a complex compound contains one or more ring in its structure .

For example; ethylene diamine is bidentate and ethylene diamine tetraacetic acid is hexadentate.

Example and uses of chelating agent

- EDTA: Ethylene diamine tetraacetate is used for the estimation of metals ions .
- EDTAH4: Ethylene diamin tetraacetic acid is used for softening water.
- Calcium Disodium Edetate: it is used in the treatment of heavy metal poisoning mostly caused by lead.

- Disodium Edetate: It is used in hypercalcemic states. It is also useful ion the treatment of cardiac arrhythmias.

1.6.2.17 Buffering agent (Goel, 2008)

These are materials which, when dissolved in solvent will enable the solution to resist any change in pH should an acid or an alkali be added. The choice of suitable buffer depends on the pH and buffering capacity required.

Features of buffering agent

It should have a low toxicity, it should be buffered at the range of 7.4 as the pH of the body is 7.4, it should be non-irritant.

Examples of buffering agent

Most of the buffering systems are based on

- Carbonate
- Citrates
- Gluconates
- Lactates
- Phosphates
- or tartrates etc.

1.6.2.18 Viscosity imparting agents (Gohel, 2015)

These agents are used when it is desirable to increase or decrease the viscosity of a liquid either to serve as adjacent for palatability or to improve pour ability. They are also called thickening agents.

Viscosity imparting agents are of two types

c. Viscosity modifier-Viscosity modifiers decrease the viscosity of a liquid to improve pour ability and make it more palatable.
d. Viscosity enhancer- Viscosity enhancers increase the viscosity of a liquid to improve pour ability and make it more palatable.

Most commonly used viscosity imparting agents are

- Hydroxyethylcellulose

- Hydroxypropylmethylcellulose
- Methylcellulose
- Polyvinyl alcohol
- Polyvinylpyrrolidone

1.6.2.19 Humectant (Smith, J. and Hong-Shum, L., 2011)

A humectant attracts and retains the moisture in the nearby air via absorption, drawing the water vapor into and/or beneath the organism/object's surface. Humectants absorb water vapors from atmosphere till a certain degree of dilution is attained. Aqueous solutions of humectants can reduce the rate of loss of moisture.

Ideal properties of humectants

- It must absorb moisture from atmosphere and retain the same under the normal conditions of atmospheric humidity.
- It should be colorless or not of too intense color.
- It should have good odor and taste.
- It should be nontoxic and nonirritant.
- It should be noncorrosive to packaging materials
- It should not solidify under normal conditions.
- It should not be too costly.

Classification of humectants with examples

There are three types of humectants such as inorganic humectants, metal organic humectants and organic humectants.

a. **Inorganic humectants**

   These are limited used in cosmetics. Calcium chloride is an example. It has compatibility problems and corrosive in nature. Hence it is not frequently used in cosmetics.

b. **Metal organic humectants**

   These are limited used in cosmetics because of compatibility problems, corrosive nature and pronounced taste. The example of this class is sodium lactate.

c. Organic humectants

These are widely used in cosmetics. They include polyhydric alcohols, their esters and ethers. The most commonly used organic humectants are glycerol, ethylene glycol, polyethylene glycol (PEG), diethylene glycol, tri ethylene glycol, propylene glycol, dipropylene glycol, glycerin, sorbitol, mannitol, glucose.

1.6.2.20 Surfactants (Richard, 2006)

Surfactants are compounds that lower the surface tension (or interfacial tension) between two liquids or between a liquid and a solid and increase the solubility. They are also known as surface active agents.

Properties of surfactants

A surfactant must fulfill two structural requirements:

a) A surfactant must contain a lipophilic region.
b) A surfactant must contain a hydrophilic region.

In a surfactant both hydrophilic and lipophilic region must be balanced because then both the regions will be concentrated at an interface and therefore surface tension will be lowered.

Types of surfactants:

There are of four types of surfactants based on the charge of the hydrophilic region:

a. Anionic surfactant

(here the hydrophilic region is negatively charged i.e. an anion) Sodium lauryl sulphate - It is used as an excipient on some dissolvable aspirins and other fiber therapy caplets.

b. Cationic surfactant

(Here hydrophilic region is positively charged i.e. a cation) Cetyl trimethyl ammonium bromide (cetrimide) - is an effective antiseptic agent against bacteria and fungi

c. Non-ionic surfactants

Tween 80 (polyoxyethylene sorbitol monooleate)- Polysorbate 80 is an excipient that is used to stabilize aqueous formulations of medications for parenteral administration Span (sorbitan ester of lauric acid)

d. Amphoteric surfactant

Lecithin- it acts as a wetting, stabilizing agent and a choline enrichment carrier, helps in emulsifications and encapsulation, and is a good dispersing agent. N-dodecyl alanine.

1.7 Some excepients used in the formulation (Rowe, Sheskey and Quinn, 2009)

1.7.1 Sodium lauryl sulfate

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

1.7.2 Lactose

Lactose is one of the earliest known binding agents to be used in tablet manufacturing process. It is a white powder without any odor or taste. Native Lactosees are available from a wide variety of plant sources such as corn, potato and wheat. However, these varieties tend to be highly viscous, to agglomerate, and have poor flow properties, making their handling difficult during the tablet manufacturing process. Newer varieties such as pregelatinized Lactose help to overcome these drawbacks because they are pre-cooked andpartly hydrolyzed during the production stage. Such varieties lend themselves well to wet granulation as well as direct compression methods of tablet manufacture. Besides, it is directly compressible diluents. It possesses good binding properties and disintegrant activity.

1.7.3 Microcrystalline Cellulose

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

1.7.4 Povidone

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

1.7.5 Magnesium Stearate

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

1.7.6 Talc

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

1.7.7 Calcium phosphates

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

1.7.8 Lactose

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

1.7.9 Polyethylene glycol (PEG)

Polyethylene glycol (PEG) is a polyether compound with many applications from industrial manufacturing to medicine. It is a high molecular weight polymer of ethylene oxide and is a blend of polymers with different degrees of polymerization. It acts as binder & dry lubricant due to its laminar structure and therefore can be used in the manufacture of pills and tablets for certain pharmaceutical preparations .The natural lubricity, low volatility and water solubility of PEGs make them useful in a wide range of lubricants (Dow, 2011).

1.5.10 Boric acid

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

1.7.11 Hydroxypropylmethylcellulose (HPMC)

Hydroxypropyl methylcellulose (HPMC) is a semisynthetic, inert substance used as alubricant, as well as an excipient and controlled-delivery component in oral medicaments, found in a variety of commercial products. HPMC is a white to light yellow powder or granular product. HPMC, a multipurpose additive for pharmaceutical, can be functioned as thickener, dispersant, emulsifier, film forming agent, etc. It is used in tablets for dressing and binding to improve solubility of the drugs. It functions as controlled release agent to delay the release of a medicinal compound into the digestive tract. It is also used as a binder and as a component of tablet coatings (Alibaba, 2013).

Chapter-II

Literature Review

2.1 Literature Review

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

In 1987 Doelker, Mordier et al., evaluated the properties of sixteen NF grade microcrystalline celluloses. The tableting characteristics of sixteen NF grade microcrystalline celluloses produced by seven manufacturers were investigated. Nine samples were type 1 celluloses (fine powders) and seven corresponded to type 2 celluloses (coarse powders). Some samples were second batches of the same products. The powders were examined for their moisture content, particle-size distribution, for their true, bulk and tap densities and for their flow properties. The effect of adding a lubricant with a low friction coefficient (0.5% magnesium stearate) on the packing and flow properties was evaluated. Basic compression studies were made on an instrumented eccentric tableting machine at an axial pressure of 100 MPa. The work of compression and the elastic recovery of the compacts were determined, as well as many friction parameters. The tabletability of the powders was assessed by measuring the diametral crushing force of the compacts (Doelker, Mordier et al., 1987).

Again they experimented in a second set of samples, they examined the effect on the compactability of the powders of adding 0.5% magnesium stearate. Weight variations of lubricated tablets were studied on a high speed rotary machine. In these runs, the force required to prepare tablets of a given mechanical strength was monitored. The uniformity of dimensions, the friability and the disintegration time of the tablets were also checked.

In 1995 Flemming and mielck took an attempt to find out the Suitability of Direct-Compression Excipients Estimated from Powder Characteristics and Flow Rates. Eleven direct-compression excipients, namely 3 microcrystalline celluloses, 4 lactoses, 4 co-processed excipients, and 4 mixtures of lactoses with Avicel PHI02 SCG were evaluated for possible use in micro tableting. Powder-technological parameters, namely particle size distributions, true and apparent densities, densification behaviour, and mass flow rates from a funnel through very narrow orifices, were determined. Flow rates required on modern high-speed rotary tableting machines were calculated. Flow rates may be estimated even for very narrow orifices, and such studies aid in selection of suitable excipients (Flemming and Mielck, 1995).

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

In August 1999 Fridrun podczeck and J. Micheal newton studied the powder with excipient filling in capsule and observed their properties on a Bosch GKF–400S tamp filling machine. These machines depend on pushing pins through a powder bed so that a unit dose is transferred into a dosing disc. This dose is then ejected into the capsule body. The results indicate that the range of powders that can be filled on this type of machine exceeds that applicable to a dosator nozzle system. Filling problems due to powder flooding could be solved by increasing the powder bed height in the powder bowl. The fact that such powders usually do not form a firm plug was not reflected in the coefficient of fill weight variation, and uniform filling could hence be achieved without problems. The influence of the powder bed height on the capsule fill weight increased with decreasing powder flow. The influence of the setting of the tamping pins on the capsule fill weight was comparatively small and further decreased with a decrease in powder flow. However, when a granulated product (Elcema G250®) was filled, the tamping pin setting was more important than the influence of the powder bed height on the capsule fill weight. For moderate flowing powders the coefficient of fill weight variation appeared to be nearly

independent of powder bed height or tamping pin setting. However, the filling performance of powders with poor flow properties could be adjusted by optimising both machine settings. Very complex relationships were found between the powder properties such as angle of internal flow, dynamic densification profile, Carr's compressibility index and particle size and shape, and the filling behavior (Podczeck & Newton, 1999).

In 2000 Michael K. Taylor , Jeri Ginsburg, Anthony J. Hickey, Ferdous Gheyas examined the flow properties of typial tablet and capsule formulation excipients, active compounds, and representative formulation with current and novel flow measurement techniques to identify a reliable bench test to quantify powder flow as a screening method in early tablet and capsule formulation development. Test methods employed were vibrating spatula, critical orifice, angle of repose, compressibility index, and avalanching analysis. Powder flow results from each method were compiled in a database, sorted, and compared. An empirical composite index was established and powder flow was ranked in accordance with formulator experience. Principal components analyses of the angle of repose, percent compressibility, and critical orifice of the powder materials were also performed. The first principal component accounted for 72.8% of data variability; scores associated with this principal component score can serve as an index of flowability. Data generated from vibrating spatula and avalanching methods were not reproducible and were inconsistent with formulator experience and cited vendor references for flow. Improvements of test instruments and further studies are necessary for better assessment of these approaches (Michael K., et al., 2000)

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

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

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

Later in 2001 Sinka, Schneider and Cocks investigated the flow behaviour of four pharmaceutical powders using a model known as shoe-die-filling system. The variation of mass delivered to the die refers to the measurement of flowability. Considering the context of pharmaceutical powders, the concept of critical velocity regarding incomplete filling was observed. The filling process was recorded using a high-speed video system. It may allow observing the different flow patterns and influences of the critical velocity. The influence of humidity for one of the powders was found to be negligible. In fact the process such as die opening and die filling and ondition of operation such as in air or vacuum significantly change the flow behavior (Sinka et al., 2001).

In 2003 Karen M., Nagel, Garnet E. & Peck investigated the effects of Excipients on the Powder Flow Characteristics of Theophylline Anhydrous Powder Formulations. Pharmaceutical excipients may have a great effect on properties affecting tablet production. To determine if formulations containing theophylline anhydrous would have properties allowing them to be easily tableted, functional parameters affecting powder flow were evaluated. The Carr Flowability Indices were used for this evaluation. Formulations to be studied include theophylline anhydrous as the active ingredient, hydrous lactose and dicalcium phosphate

dihydrate as diluents, polyvinylpyrrolidone as a binder, and fumed silica as a flow promoter. The effect of each component on powder flow is discussed (Karen M., et al., 2003).

Later in the year 2003 Matthew P Mullarney, Bruno C Hancock, Glenn T Carlson, Dauda D Ladipo and Beth A Langdon researched on the powder flow and compact mechanical properties of sucrose and three high-intensity sweeteners used in chewable tablets.The physical, flow, and mechanical properties of four common pharmaceutical sweeteners were measured to assess their relative manufacturability in solid dosage formulations. Powder flow and cohesivity as well as compact mechanical properties such as ductility, elasticity, and tensile strength were measured and found to be noticeably different. Among these sweeteners, sucrose and acesulfame potassium demonstrated excellent flowability and marginal mechanical property performance relative to over 100 commonly used pharmaceutical excipients evaluated in the authors' laboratory. Saccharin sodium and aspartame demonstrated poor flowability and superior compact strength relative to sucrose and acesulfame, despite their noticeably higher brittleness. These data suggest that careful selection of an appropriate sweetener is warranted in obtaining desirable process and tableting robustness, particularly if sweetener loading is high (Mullarney M., e al., 2003).

Later in the year 2003, Yeli Zhang, Yuet Law and Sibu Chakrabarti investigated the flowability of commonly used direct compression binders. Five classes of excipients were evaluated, including microcrystalline cellulose (MCC), Lactose, lactose, dicalcium phosphate (DCP), and sugar. In general, the Lactose category exhibited the highest moisture. DCP displayed the highest density. MCC, Lactose, lactose, and sugar had shown moderate whereas DCP had shown excellent flowability (Zhang, Law and Chakrabarti, 2003).

Later in the year of 2003 three researcher named Eetu Räsänen, Osmo Antikainen and Jouko Yliruusi found a new method to predict flowability using a microscale fluid bed. The purpose of this research was to develop a new method to predict the flow behavior of pharmaceutical powders using a multichamber microscale fluid bed. Different amounts of poorly flowing paracetamol were added to various grades of microcrystalline celluloses and silicified microcrystalline cellulose powders. Magnesium stearate was used as a lubricant. Experimental minimum fluidization velocities (u mf) were defined using 2 to 4 g (equal to 10 mL) of material.

The reference flowability of the powders was determined using a specific flow meter. Also, the weight variation of the compressed powders, using a single-punch press, was measured. When the amount of paracetamol in the excipients was increased, the experimentalu mf increased and the fluidization behavior grew worse. Principal component analysis (PCA) established that the pressure difference over the bed as a function of fluidization velocity could be used to characterize the behavior of powders. The increase in poor fluidization behavior of the powders was in accordance with the increasing amount of paracetamol and with the increasing weight variation of the tablets. Furthermore, the angle of repose and the flow rate of silicified microcrystalline cellulose powders were predicted using a partial least squares (PLS) model. The developed method to predict flowability is a promising approach for use in the preformulation and formulation stages of new drug candidates, for example (Räsänen E., et al., 2003).

In 2004 Shobha N. Bhattachar and five other researcher evaluated the vibratory feeder method for assessment of powder flow properties. The vibratory feeder method, a flow measurement technique that quantifies avalanche flow, has been adapted for measurement of the flow properties of common pharmaceutical powders used in solid oral dosage forms. The flow properties of 17 different powders were measured with the instrument, and the results are reported as a powder flow index (PFI). The PFI trends of the powders correlate well with flow properties reported in the literature. The flow properties of the powders were also measured with a commercially available avalanche instrument, the Aero-Flow™, and the results were reported as the mean time to avalanche (MTA). Since the two instruments analyze the avalanche by different algorithms, the results were compared with nonparametric statistical evaluation of ranked data, and they were found to be in excellent agreement. A recommended procedure for measurement of powder flow with the vibratory feeder is presented.

Later in the year of 2004 three researcher called I.C Sinka, L.C.R Schneider and A.C.F Cocks tested on the flow properties of powders with special reference to die fill. The flow behaviour of four pharmaceutical powders was investigated using a model shoe-die-filling system. The variation of mass delivered to the die as a function of shoe velocity provides a measure of flowability. The paper discusses the concept of critical velocity, above which incomplete filling is observed, in the context of pharmaceutical powders. The filling process was recorded using a

high-speed video system, which allowed the different flow patterns to be observed, and how this influences the critical velocity to be evaluated. The influence of humidity, which was investigated in detail for one of the powders, was found to be small. The initial conditioning of the material, the die opening and if die filling takes place in air or in vacuum, however, were found to change the flow behaviour significantly (Sinka I., et al., 2004).

In 2005 Nitin A., Bhimte, Pralhad T. & Tayade evaluated the property of Microcrystalline Cellulose Prepared From Sisal Fibers as a tablet excipient. There were variations in the force necessary to compact thevarious mixtures, especially when MCC was used as a dil-uent. This type of variation in the force was not prominent when the MCC was used as a disintegrant. In the case of tablets prepared with MCC and carrageenan, the tablets of sisal fiber MCC showed a similar release pro-file to tablets of other commercial MCCs in all 3 proportions used (1:0.5, 1:1, and 1:1.5, data not shown). The drug release was most sustained in the tablets prepared with 1:1.5 pro-portions. The above data suggest that MCC prepared with sisal fibers is completely miscible with sustained-release vehicles and could be used as an adjuvant in controlled-release formulations. The above data demonstrated that MCC derived from sisal fibers could be an industrially feasible alternative for currently used MCCs as diluent and disintegrant for both immediate-release as well as sustained-release oral solid dosage forms.

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

In 2006, Bagster and Crooks 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 (Bagster and Crooks, 2006).

In 2007 Abdul Mobeen N. Faqih and three other scientist took an attempt to evaluate the effect of moisture and magnesium stearate on flow properties of cohesive materials. In this article the gravitational displacement rheometer (GDR) is used to characterize the effects of formulation composition and environmental conditions (moisture) on flow properties of cohesive pharmaceutical powders under unconfined conditions. The amount of moisture in the sample often has important effects on the physical and chemical properties of pharmaceutical solids. Properties such as flow, compaction, disintegration, dissolution, hardness and chemical stability are all influenced by moisture. In the case of lactose, as moisture content increases in the powder bed, the flowability becomes poorer as the moisture condenses on the surface and increases cohesion. The celluloses show opposite effect as compared to lactose. Here, as moisture content increases, the flow properties improve dramatically. The GDR also captures the effect of lubricant concentration on the cohesion of powders. The presence of lubricant does not play any significant impact for free flowing powders, but as powder cohesion increases, the lubricants allow for improved flowability of powders. The GDR was also used for a case study of real drug formulation. The methodology was able to evaluate the impact of humidity and lubricant concentration on the flow properties of the formulation.

In 2008 Rakhi B., Mobin A. & Mansoor A. researched on Comparative Evaluation of Flow for Pharmaceutical excipients. The objective of the present work was to carry out a systematic evaluation of flow of pharmaceutical powders and granules using compendial and non-compendial methods. Angle of repose, bulk density, tapped density, Carr's compressibility index, and Hausner ratios were evaluated. Additionally, flow was characterized using a powder rheometer in which a sensitive force transducer monitors the forces generated as a result of the sample displacement. The critical attributes such as cohesivity index, caking strength, and flow stability were determined for samples. The samples consisted of different grades of magnesium stearate powder including bovine, vegetable, and food grade, physical mixture powder blend

consisting of a model formulation, granules prepared by various methods including slugging, high shear granulator, and fluid bed dryer. Lubricant efficiency was also determined for granules lubricated with various concentrations of magnesium stearate. 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. The flow stability test determined that the powders were not affected by the test conditions on the rheometer. The non-compendial tests were discriminating to even minor variations in powder flow (Rakhi B., et al., 2008).

In the same year (2008) two researcher named Hao Hou and Changquan Calvin Sun researched on the Quantifying effects of particulate properties on powder flow properties using a ring shear tester. Effects of particle size, morphology, particle density, and surface silicification, on powder flow properties were investigated using a ring shear tester. Flow properties were quantified by flow function (FF), that is, unconfined yield strength, fc, as a function of major principal stress. A total of 11 powders from three series of microcrystalline cellulose (MCC): Avicel (regular MCC, elongated particles), Prosolv (silicified MCC, elongated particles), and Celphere (spherical MCC), were studied. Particle size distribution in each type of MCC was systematically different. Within each series, smaller particles always led to poorer powder flow properties. The slope of FF line was correlated to degree of powder consolidation by external stress. A key mechanism of the detrimental effect of particle size reduction on flow properties was the larger powder specific surface area. Flow properties of Celphere were significantly better than Avicel of comparable particles size, suggesting spherical morphology promoted better powder flow properties. Flow properties of powders different in densities but similar in particle size, shape, and surface properties were similar. When corrected for density effect, higher particle density corresponded to better flow behavior. Surface silicification significantly improved flow properties of finer MCC, but did not improve those of coarser (Hou & Sun, 2008).

In 2009 Kalyana C. Pingali and three other researcher took an attempt to improve the flow property of API. The ‘formulation’ approach used here focuses on enhancing flow properties of three chemically different drug powders (micronized acetaminophen, levalbuterol tartrate, and didesmethylsibutramine tartrate) by using small amounts of lubricants, glidants, and other

additives, both individually and in combination. Additives are intimately mixed using a laboratory-scale V-blender with an intensifier bar. Flow index, dilation, and electrical impedance were measured for a total of 24 blends.*Results*: The flow behavior of all three APIs improved with the addition of these additives. Relative effectiveness of different additive combinations displayed remarkable consistency for all three APIs. Simultaneous presence of SiO2, MgSt, and talc led to substantial decreases in cohesiveness, causing major improvements in flowability of powder. All three properties showed a very tight correlation. *Conclusions*: Drug powders with improved flow were found to exhibit low dilation and low impedance values. A common linear correlation between flow index and impedance and also between dilation and impedance was observed for all three APIs, indicating that electric properties play a substantial role in the cohesivity of all three APIs, and suggesting the presence of a common mechanism for the emergence (and mitigation) of cohesive phenomena (Kalyana C., et al., 2009).

Later in the year of 2009 Snežana Savic and his crew researched on Influence of different lipophilic excipients on *in vitro*/*in vivo* skin performance. This study focuses on the properties of topical vehicles based on alkylpolyglucoside natural surfactant-mixed emulsifier, cetearyl glucoside and cetearyl alcohol, in order to propose their use as "ready to use" pharmaceutical bases for a number of model drugs. The results have shown that the emulsion vehicles consisted of a complex colloidal structure of lamellar liquid crystalline and lamellar gel crystalline type. Varying of lipophilic excipient influenced noteworthy variations in the colloidal structure demonstrated as different rheological profiles accompanied to the certain degree by different water distribution modes, but notably provoked by drug nature (an amphiphilic electrolyte drug vs. nonelectrolyte). *In vitro* permeation data obtained using ASC membranes in an infinite dose-type of experiment stressed the importance of the vehicle/solute interactions in case of small variation in formulation composition, asserting the drug properties in the first hours of permeation and rheological profile of the vehicles in the later phase of experiment as decisive factors. *In vitro* skin irritation test demonstrated a mild nature of the emulsifying wax and the absence of negative effects of used oil phases on cell viability in formulation concentrations correspondent to the therapeutic need. This result alongside with data obtained from *in vivo* study, could additionally promote investigated topical vehicles as prospective "ready to use" pharmaceutical bases (Savic S., et al., 2009).

Again in 2009, Meer Saiful Hassan and Raymond Wai Man Lau 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 (Hassan and Raymond, 2009).

In 2010 Mafalda C., Sarraguca and five other researcher evaluated the flow properties of Pharmaceutical powders by using near IR spectroscopy. The physical properties of pharmaceutical powders are of upmost importance in the pharmaceutical industry. Powders flow properties are measured using a number of parameters such as, angle of repose, compressibility index (Carr's index) and Hausner ratio. To estimate these properties, specific and expensive equipment with time-consuming analysis is required. Near infrared spectroscopy is a fast and low-cost analytical technique thoroughly used in the pharmaceutical industry in the quantification and qualification of products. To establish the potential of this technique to determine the parameters associated with the flow properties of pharmaceutical powders, blended powders based on paracetamol as the active pharmaceutical ingredient were constructed in pilot scale. Spectra were recorded on a Fourier-transform near infrared spectrometer in reflectance mode. The parameters studied were the angle of repose, aerated and tapped bulk density. The correlation between the reference method values and the near infrared spectrum was performed by partial least squares and optimized in terms of latent variables using cross-validation. The near infrared based properties predictions were compared with the reference methods results. Prediction errors, which varied between 2.35% for the angle of repose, 2.51% for the tapped density and 3.18% for the aerated density, show the potential of NIR spectroscopy in the determination of physical properties affecting the flowability of pharmaceutical powders (Mafalda C., et al., 2010).

Later in the same year, 2010 two scientist Venkateshwar Rao Nalluri and Martin Kuentz researched on the Flowability characteristics of drug excipient using a novel method. The scope of the work is twofold, first to introduce a new avalanche testing instrument and secondly to

characterise flowability of pharmaceutical blends comprising of coarse and fine particles. The results were compared with established powder characterisation instruments like the angular shear cell and a flow through orifice tester. These different methods were applied to a broad concentration range of binary mixtures comprising coarse, well-flowing lactose and micronised, poorly flowing albendazole. Some of the mixtures were further analysed with scanning electron microscopy. The results showed clear changes in the flow behaviour of the mixtures that were considered as critical flow concentrations (CFCs). At least three drug concentrations were observed for which the flow behaviour essentially changed. Accordingly, different flow regions were identified, which were explained on the basis of changed particle packing configurations. A theoretical model successfully provided a first estimation of the initial two CFCs. In conclusion, the novel avalanche testing instrument provided complementary information to conventional flowability methodologies, and a thorough assessment of pharmaceutical blends is needed to avoid CFCs in view of a robust formulation development and hence with respect to building quality into the design of the solid dosage forms (Nalluri & Kuentz, 2010).

Again in 2010, Gerald Gold studied the commonly used glidants, fumed silicon dioxide, magnesium stearate, Lactose, and talc in combination with selected materials. Many of the more widely used glidants actually decreased the flow rate. Glidants which lowered the angle of repose did not necessarily increase the flow rate. Flow rate were not always detectable by angle of repose measurement. By doing the comparison of the angle of repose and the flow rate they suggested that the angle of repose was not a reliable method for evaluating the flow of these materials (Gold, et al., 2006).

In the same year 2010 Ganesh Shete researched on the flow behaviour of binary mixtures of paracetamol and different grades of microcrystalline cellulose. As expected, the flowability of the samples was affected both by the amount of paracetamol and the physical properties of microcrystalline celluloses (MCC) and the mixtures. The effect of lubricant varied depending on the MCC grade: magnesium stearate was able to improve the flowability of the mixtures containing PH102 and PH200 while it did not affect the flowability of PH101. This is likely to be due to the high carrier payload of PH101. Thus, magnesium stearate is not able to coat the PH101 particles. Multivariate analysis showed that the flow of the binary excipient-drug

mixtures through an orifice is affected by several phenomena, such as charging, surface moisture, carrier payload and particle size (Shete G., 2010).

Also in 2010 Jin Lee studied on the Physicochemical Properties of Excipients and Powders and Tablet Characterization. It is known that tablet is a major category of solid dosage forms which are widely used worldwide. Based on preformulation studies, the optimal dosage forms are generally decided. This article focuses on general preformulation approaches for tablet production, physicochemical properties of drug and excipients, and types and functions of excipients used for tablet formulation and drug excipient incompatibility (Lee J., 2010).

In 2011 Sayantan Chattoraj, Limin Shi and Changquan Calvin Sun tested for improving flow properties of a cohesive cellulose powder by surface coating with nano-silica through comilling. Poor flow properties hinder the easy handling of powders during industrial-scale processing. In this work, we show that powder flow can be substantially improved by reducing the cohesion of powders by coating them with nanosized guest particles. We further show that comilling is an efficient process for nanocoating. We have systematically investigated the effects of total number of comilling cycles (10–70 cycles) and silica loading (0–1.0 wt %) on the flow behavior of a highly cohesive and poorly flowing grade of microcrystalline cellulose powder (Avicel PH105). Optimum flow enhancement has been achieved with 1.0 wt % silica loading at 40 comilling cycles. 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. Comilling is fast and suitable for continuous processing. It shows potential for addressing industrial powder handling problems caused by poor powder flow properties (Chattoraj S., et al., 2011).

In 2012 three researcher named PD. Chaudhari, AA. Phatak and Ujwala Desai took an attempt to find out excipient as an alternative to novel chemical entities and their flow properties. In addition to this the cost involved in development of new chemical excipients with improved properties is quite high. In response to these deficiencies, drug formulation scientists have relied on increasing numbers of combination excipients introduced by excipient manufacturers into the commercial market.In order to justify the high rise in new drug development and high industrial output demand, new excipients with purpose satisfying characteristics are the need of the

hour.New combinations of existing excipients are an interesting option for improving excipient functionality now-a-days. The current review article is prepared to have a look over the recent development in excipient technology and the approaches involved in development of such excipients. Particle engineering of individual excipients and excipient combinations using coprocessing,by virtue of subparticle modifications,has provided an attractive tool for developing high functionality excipients that are suited to modern tablet manufacturing processes.It signifies the synergistic outcome of the combination of excipients taking their material property into consideration. It also emphasises on the particular material properties in terms of physico-mechanical that are useful to overcome the limitation of existing excipients. The future scope determines that coprocessed excipients are the rising need of 21st century (Chaudhari PD., et al 2012).

Later In 2012 Behin Sundara Raj, Punitha I.S.R. and Suraj Dube researched on the formulation and Characterization of Fast Disintegrating tablets of Amlodipine using Super disintegrants. Amlodipine is a sparingly soluble orally administered drug and the rate of absorption is often controlled by the rate of dissolution. The rate of dissolution will increase by incorporating the drug in a fast dissolving dosage form. An attempt will be made to develop rapidly disintegrating oral tablets of Amlodipine Besylate by direct compression method. In this study, Fast Dissolving Tablet (FDT) was prepared using direct compression method using Crospovidone and Sodium Lactose glycolate as the super disintegrants. Amongst all formulations, formulation F3 prepared by a combination of both Crospovidone and Sodium Lactose glycolate showed least disintegrating time, and faster dissolution of 87%. Combination of super disintegrants were found to be better to formulate fast dissolving tablets of Amlodipine besylate (Raj B., et al., 2012).

Again in 2012 Laila J. Jallo, Chinmay Ghoroi, Lakxmi Gurumurthy, Utsav Patel and Rajesh N. Dave researched flow and bulk density of pharmaceutical powders using surface modification. A limited design of experiment was conducted to establish a standardized dry coating procedure that limits the extent of powder attrition, while providing the most consistent improvement in angle of repose (AOR). The magnetically assisted impaction coating (MAIC) was considered as a model dry-coater for pharmaceutical powders; ibuprofen, acetaminophen,

and ascorbic acid. Dry coated drug powders were characterized by AOR, particle size as a function of dispersion pressure, particle size distribution, conditioned bulk density (CBD), Carr index (CI), flow function coefficient (FFC), cohesion coefficient using different instruments, including a shear cell in the Freeman FT4 powder rheometer, and Hansen flowability index. Substantial improvement was observed in all the measured properties after dry coating relative to the uncoated powders, such that each powder moved from a poorer to a better flow classification and showed improved dispersion. The material intrinsic property such as cohesion, plotted as a function of particle size, gave a trend similar to those of bulk flow properties, AOR and CI. Property improvement is also illustrated in a phase map of inverse cohesion (or FFC) as a function of bulk density, which also indicated a significant positive shift due to dry coating. It is hoped that such phase maps are useful in manufacturing decisions regarding the need for dry coating, which will allow moving from wet granulation to roller compaction or to direct compression based formulations (Jallo J., et al., 2012).

In 2013 two scientist named Juan G. Osorioa & Fernando J. Muzzio researched on the effects of powder flow properties on capsule filling weight uniformity. The purpose of this study was to develop effective laboratory methods for characterizing flow properties of pharmaceutical powder blends and correlating such properties to weight variability in filled capsules. The methods used for powder flow characterization were bulk and tapped density, gravitational displacement rheometer (GDR) flow index, Freeman Technology V.4 (FT4) powder rheometer compressibility, FT4 basic flow energy (BFE), and cohesion parameters [cohesion, (C) and flow factor (ffc)] measured in a shear cell also using the FT4. Capsules were filled using an MG2-G140 continuous nozzle dosator capsule-filling machine. Powder flow properties were the most predominant factors affecting the weight and weight variability in the filled capsules. Results showed that the weight variability decreased with increasing bulk and tapped density, ffc and BFE, while the weight variability increased with increasing compressibility, cohesion and GDR flow index. Powder flow properties of the final blends were significantly correlated to the final capsule weight and weight variability of the filled capsules (Juan G., et al., 2013).

In the same year (2013), Traina and other five researcher from Belgium 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 (Trainaa, et al., 2013).

Again in the same year of 2013, Silva and Splendor 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 (Silva and Splendor, 2013).

In 2014 *Karina Ivonne Fuentes-gonzÁlez, Leopoldo Villafuerte-robles worked on the topic of* powder flowability as a functionality parameter of the excipient. The evaluated parameters were the powder flow through different size orifices and the compressibility index, as absolute values and as values relative to Helmcel 200. The parameters determined with pure excipients and in mixtures with a model drug, metronidazole.Results: The compressibility index is a specific measurement for each powders blend that allows the assessment of its overall flow properties. Flowability, expressed as the flow rate, shows so many different results as orifices are being tested. Both methods exhibit comparable results only by wide orifice sizes where the interaction with de orifice walls is minimized. The flow rate increases progressively, mostly in a potential relationship, with an increasing orifice diameter. The flow rate of GalenIQ 720 attains a maximum with 0.4-0.8% magnesium stearate.Formulations containing GalenIQ 720 show about 2.8 times greater flowability than those containing Helmcel 200 while the flowability of GalenIQ 720 is about 8.7 times greater than that of Helmcel. The presence of metronidazole attenuates the differences observed by the flowability of pure excipients and its spread.Conclusion: Both methods consistently show a comparable improvement of metronidazole flowability with GalenIQ 720 and a deterioration of the same with Helmcel 200. The knowledge of the individual materials flowability allows the inference of their effect on the flowability of their mixtures but not the magnitude of this effect (*GonzÁlez K., et al., 2014)*.

Chapter-III

Materials and Method

3.1 MATERIALS

3.1.1 Excipients Collection

For the research purpose different classes of excipients were collected from the different labs of Pharmacy Dept. of East West University. Our respected supervisor Md. Faisal Bin Karim, Lecturer and Co-supervisor Md. Anisur Rahman, Senior Lecturer, Department of Pharmacy, East West University send a requisition letter to the authority for some specific excipients and after few months we got most of the ingredient we asked for.

3.1.2 Excipients

The list of excipients those were used during this research is given below with their individual source (supplier name):

Table 3.1 : List of excipients through this research work.

SL no.	Name of Excipients	Source (Supplier Name)
1.	Lactose	MERK, Germany
2.	CMC	MERK, Germany
3.	Zn Stearate	MERK, Germany
4.	Talc	MERK, Germany
5.	Polyethelyne Glycol	MERK, Germany

3.1.3 Equipments and Instruments

Table 3.2: List of instruments through this research work

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

3.1.4 Images of Instruments (East West University)

Some image of important instruments those were used in different tests during research work

Figure 3.1: Mixture Machine

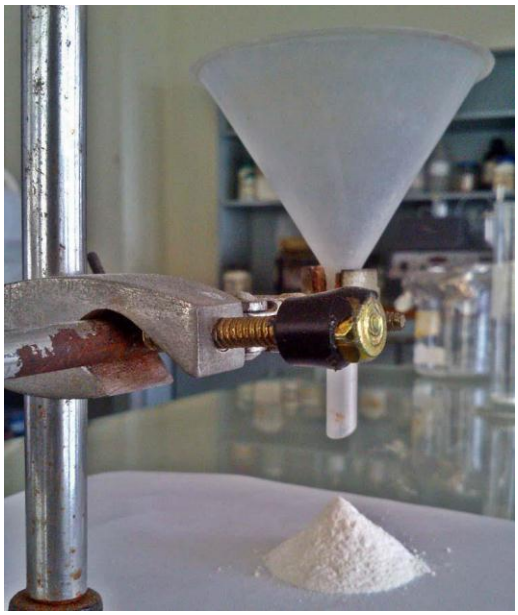


Figure 3.2: Stand clamp with funnel

Figure 3.4: Double Cone Blender

Figure 3.5: Electronic Balance (Austscientific, 2015)

3.1.5 Apparatus

The apparatus that were used in this experiment are described below.

Table 3.3: List of apparatus used throughout this research work

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

3.2 METHODS

3.2.1 Density

Granule density, True Density, Bulk Density may influence compressibility, tablet porosity, flow property, dissolution and other properties. Higher compression load was required in case of dense and hard granules which in turn increases the tablet disintegration and drug dissolution times. Density is usually determined by Pycnometer (USP29-NF24, 2013).

3.2.2 Preparation of various set of formulas

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

3.2.3 Preparation of mixture of formula and constant excipient

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

3.2.4 Flow property measurement

3.2.4.1 Determination of bulk volume

- At first the mixture of materials in a test tube was transferred to a dry measuring cylinder.
- The volume was measured after manually tapping the cylinder about 2 times on a flat table top surface.
- The achieved volume is the bulk volume which was documented.

3.2.4.2 Determination of tapped volume

- After measuring the bulk volume, the mixture of materials in the measuring cylinder was tapped manually 20 times and above until little further volume change is observed.
- The tapping is achieved by raising the cylinder and allowing it to drop under a specified distance.
- The measured volume was documented

3.2.4.3 Calculation of Carr's index and Hausner ratio

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

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

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

(Merriam, 2013)

Where,

V_o= Bulk volume

V_f = Tapped volume

3.3 ANGLE OF REPOSE

The angle of repose is used in the several branches of science to characterize the flow properties of solids. Angle of repose is interring particulate friction or resistance to movement between particles. Angle of repose test results is reported to be very dependent upon the method used. Experimental difficulties arise as a result of segregation of material and consolidation or aeration of the powder as the cone is formed. The method continues to be used in the pharmaceutical industry. The angle of repose contains, three-dimensional angle (relative to the horizontal base) supposed by a cone shape (USP29-NF24, 2013).

3.3.1 Basic Methods for Angle of Repose

A variety of angle of repose test methods are described in these part. The most common method static angle of repose can be determined and it can be classified on the basis of the following two important experimental variables:

1. The powder passes from the height of the funnel which is fixed relative to the base, or the height may be varied as the pile forms.
2. The base diameter of the pile may be fixed or the diameter of the powder cone may be varied as the pile forms.

3.3.2 Variations in Angle of Repose Methods

In addition to the above methods, the following variations are used to some extent in the pharmaceutical literature:

- Drained angle of repose is determined by allowing an excess quantity of material positioned above a fixed diameter base to "drain from the container. Formation of a cone of powder on the fixed diameter base allows determination of the drained angle of repose.

- The filling of a cylinder (with a clear, flat cover on one end) and its rotation at a specified speeds is determined the dynamic angle of repose. It is the angle (relative to the horizontal) formed by the flowing powder. The internal angle of kinetic friction is defined by the plane separating those particles sliding down the top layer of the powder

.Those particles that are rotating with the drum (with roughened surface) (USP29-NF24, 2013).

3.3.3 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 500that were manufactured satisfactorily, when the angle of repose exceeds 500. The flow is rarely acceptable for manufacturing purposes (USP29-NF24, 2013).

3.3.4 Experimental 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 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).

3.3.5 Measurement of Angle of repose

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

3.3.5.1 Procedure

- First of all, funnel made of plastic, glass or stainless steel was set with the holding stand tightly.
- The funnel was fixed in a place, 4 cm above the bench surface.
- On the bench surface, a piece of paper was placed.

- The mixture of the running test tube was poured through the funnel without incorporating external pressure or stress.
- The powder mixture formed a cone on the paper.
- After the cone from 5g of sample was built, height of the granules forming the cone (h) in cm and the radius (r) of the base in cm were measured.
- The angle of repose was calculated by the given formula and documented

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

(Merriam, 2013)

Where

h = height of the powder cone from the base

r = radius of the conical pile.

3.4 Preparation of Formulas

3.4.1 Preparation of Formula 1(F2)

Table 3.4: The following amounts of excipients (given with their use) were taken for the preparation of Formula 1 (F1) 10g.

Ingredients Name	Purpose of Use	Percentage	Quantity
PEG	Filler	35%	3.5
CMC	Binder	25%	2.5
Zn Stearate	Antiadherent	20%	2
Talc	Diluents	20%	2
		Total=100%	Total=10g

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

3.5 Table: The amount of lactose and F1 in different ratio (Set-1) in 3g

Ratio	Lactose:F1	Amount of lactose:F1
1	45% : 55%	1.35 : 1.65
2	55% : 45%	1.65 : 1.35
3	65% : 35%	1.95 : 1.05
4	75 : 25%	2.25 : 0.75
5	85% : 15%	2.55 : 0.45

3.4.2 Preparation of Formula 2 (F2)

Table 3.6: The following amounts of excipients (given with their use) were taken for the preparation of Formula 1 (F1) 10g.

Ingredients Name	Purpose of Use	Percentage	Quantity
PEG	Filler	25%	2.5
CMC	Binder	30%	3
Zn Stearate	Antiadherent	18%	1.8
Talc	Diluents	27%	2.7
		Total=100%	Total=10g

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

Table 3.7: The amount of lactose and F1 in different ratio (Set-2) in 3g

Ratio	Lactose:F1 (%)	Amount of lactose:F1 (gm)
1	30% : 70%	0.9 : 2.1
2	40% : 60%	1.2 : 1.8
3	50% : 50%	1.5 : 1.5
4	60% : 40%	1.8 : 1.2
5	70% : 30%	2.1 : 0.9

3.4.3 Preparation of Formula 3 (F3)

Table 3.8: The following amounts of excipients (given with their use) were taken for the preparation of Formula 1 (F1) 10g.

Ingredients Name	Purpose of Use	Percentage	Quantity
PEG	Filler	25%	2.5
CMC	Binder	30%	3
Zn Stearate	Antiadherent	18%	1.8
Talc	Diluents	27%	2.7
		Total=100%	Total=10g

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

Table 3.9: The amount of lactose and F1 in different ratio (Set-3) in 3g

Ratio	Lactose:F1 (%)	Amount of lactose:F1 (gm)
1	55% : 45%	1.65 : 1.35
2	65% : 35%	1.95 : 1.05
3	75% : 25%	2.25 : 0.75
4	85% : 15%	2.55 : 0.45
5	95% : 5%	2.85 : 0.15

3.4.4 Preparation of amlodipine set-1

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. I had assumed 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.

Table 3.10: Amlodipine Containing Different Ratios (Amlodipine Set-1) in 3g.

Ratio	Lactose : F	Amount of Lactose : F (g)	Amlodipine added (g)
1	13% : 87%	0.39 : 2.61	0.0875
2	17% : 83%	0.51 : 2.49	0.0875
3	21% : 79%	0.63 : 2.37	0.0875
4	29% : 71%	0.87 : 2.13	0.0875
5	33% : 67%	0.99 : 2.01	0.0875

3.4.5 Preparation of amlodipine set-2

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. I had assumed 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.

Table 3.11: Amlodipine Containing Different Ratios (Amlodipine Set-2) in 3g.

Ratio	Lactose : F	Amount of Lactose : F (g)	Amlodipine added (g)
1	5% : 95%	0.15 : 2.85	0.0875
2	10% : 90%	0.30 : 2.70	0.0875
3	15% : 85%	0.45 : 2.55	0.0875
4	20% : 70%	0.60 : 2.40	0.0875
5	25% : 75%	0.75 : 2.25	0.0875

3.4.6 Preparation of amlodipine set-3

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. I had assumed 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.

Table 3.12: Amlodipine Containing different ratios (Amlodipine Set-3) in 3g.

Ratio	Lactose : F	Amount of Lactose : F (g)	Amlodipine added (g)
1	7% : 95%	0.21 : 2.79	0.0875
2	27% : 73%	0.81 : 2.19	0.0875
3	30% : 70%	0.90 : 2.10	0.0875
4	35% : 65%	1.05 : 1.95	0.0875
5	40% : 60%	1.22 : 1.80	0.0875

3.4.7 Preparation of Propranolon set-1

Each ratio of the set-1 was divided to two equal portions. Each portion contains about 1.5 g of mixture. Propanolol HCl was added to each ratio of set-1. I had assumed 80 mg of Propanolol HCl tablet contain 5 mg of Propanolol HCl. 1.4 g or 1400 mg contain 87.5 mg or .0875 g of Propanolol HCl.

Table 3.13: Propranolol Containing Different Ratios (Propanolol Set-1) in 3g.

Ratio	lactose% : F%	Amount of lactose : F (gm)	Propanolol HCl added (gm)
1	13% : 87%	0.39 : 2.61	0.0875
2	17% : 83%	0.51 : 2.49	0.0875
3	21% : 79%	0.63 : 2.37	0.0875

4	29% : 71%	0.87 : 2.13	0.0875
5	33% : 67%	0.99 : 2.01	0.0875

3.4.8 Preparation of Propranolon set-2

Each ratio of the set-2 was divided to two equal portions. Each portion contains about 1.5 g of mixture. Propanolol HCl was added to each ratio of set-1. I had assumed 80 mg of Propanolol HCl tablet contain 5 mg of Propanolol HCl. 1.4 g or 1400 mg contain 87.5 mg or .0875 g of Propanolol HCl.

Table 3.14: Amlodipine Containing Different Ratios (Propanolol Set-2) in 3g.

Ratio	lactose% : F%	Amount of lactose : F (gm)	Propanolol HCl added (gm)
1	5% : 95%	0.15 : 2.85	0.0875
2	10% : 90%	0.30 : 2.70	0.0875
3	15% : 85%	0.45 : 2.55	0.0875
4	20% : 70%	0.60 : 2.40	0.0875
5	25% : 75%	0.75 : 2.25	0.0875

3.4.9 Preparation of Propranolon set-3

Each ratio of the set-3 was divided to two equal portions. Each portion contains about 1.5 g of mixture. Propanolol HCl was added to each ratio of set-1. I had assumed 80 mg of Propanolol HCl tablet contain 5 mg of Propanolol HCl. 1.4 g or 1400 mg contain 87.5 mg or .0875 g of Propanolol HCl.

Table 3.15: Amlodipine Containing Different Ratios (Propanolol Set-3) in 3g

Ratio	lactose% : F%	Amount of lactose : F (gm)	Propanolol HCl added (gm)
1	7% : 95%	0.21 : 2.79	0.0875
2	27% : 73%	0.81 : 2.19	0.0875
3	30% : 70%	0.90 : 2.10	0.0875
4	35% : 65%	1.05 : 1.95	0.0875
5	40% : 60%	1.22 : 1.80	0.0875

Chapter-IV

Results

RESULTS

4.1 Calculation of flow property of the prepared mixture ratio of diluents and formulas

4.1.1 Results of the ratos of set 1(Lactose formula 1)

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

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

Ratio	Bulk Volume, V_1 (ml)	Most Acceptable Value of V_o(ml)	Tapped Volume, V2 (ml)	Most Acceptable value of V_r(ml)	Hausner's Ratio V_0/V_r	Compressibility index $100\times(V_0-V_r)/V_0$
1	8.38	8.36	6.10	6.04	1.38	27.75
	8.41		5.90			
	8.31		6.10			
2	9.82	9.10	6.50	6.80	1.33	25.2
	8.80		6.90			
	8.90		7.00			
3	8.52	8.90	6.50	6.70	1.30	24.7
	9.00		6.90			
	9.40		6.70			
4	8.90	8.90	6.91	6.97	1.27	21.6
	8.80		7.00			
	9.20		6.90			
5	8.90	9.00	7.00	7.30	1.23	13.6
	9.10		7.50			
	9.00		7.00			

4.1.2 Angle of Repose Measurement for the ratios of Set-1(Lactose formula 1)

The angle of repose of set-1 was calculated by their cone height and radius which were measured 5 times and the average value was taken. The observed value is given below:

4.2 Table: Calculation of Angle of repose for set 1

Ratio	Height (h) cm	Avg. Height (h) cm	Radius (r) cm	Average Radius (r) cm	Angle of Repose(^{0})
Ratio 1	2.3	1.95	3.72	3.50	29.12
	2.16		3.71		
	1.8		3.2		
	1.9		3.53		
	1.6		3.46		
Ratio 2	2.2	1.70	3.03	3.20	27.97
	1.6		3.68		
	1.4		3.20		
	1.6		3.20		
	1.7		2.91		
Ratio 3	1.6	1.48	3.02	3.18	24.95
	1.3		3.17		
	1.4		3.03		
	1.4		3.23		
	1.7		3.28		
Ratio 4	1.5	1.54	3.28	3.29	25.08
	1.6		3.12		
	1.6		3.26		
	1.4		3.90		
	1.6		2.90		
Ratio 5	1.4	1.40	3.13	3.21	23.16
	1.5		3.25		
	1.5		3.17		
	1.3		3.33		
	1.3		3.21		

4.1.3 Results of the ratios of set 2(Lactose formula 2)

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

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

Ratio	Bulk Volume, V_1 (ml)	Most Acceptable Value of V_o(ml)	Tapped Volume, V2 (ml)	Most Acceptable value of V_r(ml)	Hausner's Ratio V_0/V_r	Compressibility index $100\times(V_0-V_r)/V_0$
1	7.7	8.16	5.7	5.03	1.62	38.35
	8.6		5.3			
	8.5		5.1			
2	8.4	8.50	4.9	5.43	1.56	36.11
	8.9		5.9			
	8.2		5.5			
3	8.1	8.16	5.4	5.26	1.55	35.53
	8.4		4.7			
	8.0		5.7			
4	7.9	7.73	5.2	5.16	1.49	33.24
	7.1		5.1			
	8.2		5.2			
5	8.3	8.30	5.9	5.63	1.47	32.16
	8.7		5.7			
	7.9		5.35			

4.1.4 Angle of Repose Measurement for The Ratios of Set-2(Lactose formula 2)

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

4.4 Table: Calculation of Angle of repose for set 2

Ratio	Height (h) cm	Avg. Height (h) cm	Radius (r) cm	Average Radius (r)cm	Angle of Repose (^{0})
Ratio 1	1.6	1.48	2.94	2.67	28.70
	1.5		2.89		
	1.5		2.5		
	1.4		2.53		
	1.4		2.6		
Ratio 2	1.4	1.34	2.6	2.65	26.05
	1.3		2.67		
	1.3		2.57		
	1.4		2.7		
	1.3		2.69		
Ratio 3	1.3	1.26	2.70	2.73	24.47
	1.3		2.83		
	1.1		2.62		
	1.3		2.82		
	1.3		2.68		
Ratio 4	1.3	1.26	2.80	2.85	23.15
	1.3		2.80		
	1.3		2.98		
	1.2		2.95		
	1.2		2.73		
Ratio 5	1.3	1.18	2.98	2.96	21.73
	1.1		2.93		
	1.1		2.98		
	1.3		2.91		
	1.1		2.98		

4.1.5 Results of the ratios of set 3(Lactose formula 3)

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

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

Ratio	Bulk Volume,V_1 (ml)	Most Acceptable Value of V_o(ml)	Tapped Volume, V2 (ml)	Most Acceptable value of V_r(ml)	Hausner's Ratio V_0/V_r	Compressibility index $100\times(V_0-V_r)/V_0$
1	8.8	8.6	4.9	4.7	1.82	45.3
	8.4		4.5			
	8.6		4.7			
2	8.1	8.1	4.7	4.63	1.74	42.83
	8.0		4.7			
	8.2		4.5			
3	8.2	7.77	5	4.93	1.58	36.55
	7.9		4.9			
	7.2		4.9			
4	7.5	7.3	5.0	5.0	1.46	31.50
	7.4		5.1			
	7.0		4.9			
5	6.8	6.87	5.2	5.0	1.37	27.22
	7.8		4.9			
	6.0		4.9			

4.1.6 Angle of Repose Measurement for the Ratios of Set 3(Lactose formula 3)

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

4.6 Table: Calculation of Angle of repose for set 3

Ratio	Height (h) cm	Avg. Height (h) cm	Radius (r) cm	Avg. Radius(r) cm	Angle of Repose (^{0})
Ratio 1	1.3	1.37	2.40	2.26	31.22
	1.3		2.10		
	1.5		2.50		
	1.3		2.20		
	1.4		2.10		
Ratio 2	1.4	1.38	2.85	2.56	28.32
	1.4		2.80		
	1.3		2.17		
	1.5		2.85		
	1.4		2.15		
Ratio 3	1.4	1.40	2.86	2.90	25.52
	1.3		2.92		
	1.4		3.08		
	1.4		2.78		
	1.5		2.88		
Ratio 4	1.2	1.30	2.98	2.94	23.85
	1.4		2.87		
	1.3		2.97		
	1.3		2.97		
	1.3		2.91		
Ratio 5	1.1	1.18	3.20	3.04	21.21
	1.2		2.90		
	1.3		3.10		
	1.1		3.00		
	1.2		3.00		

4.1.7 Results of the ratios of set Amlodipine set-1

For calculating Carr's index and Hausner ratio for the mixed quantity of amlodipine and formula 1, their individual bulk volume and tapped volume were measured five times and the average value was taken. The observed value is given below

Table 4.7: Calculation of Carr's index and Hausner ratio for amlodipine set-1

Ratio	Bulk Volume,V_1 (ml)	Most Acceptable Value of V_o(ml)	Tapped Volume, V2 (ml)	Most Acceptable value of V_r(ml)	Hausner's Ratio V_0/V_r	Compressibility index $100\times(V_0-V_r)/V_0$
1	3.5	3.6	2.50	2.50	1.44	30.55
	3.7		2.40			
	3.6		2.60			
2	3.9	3.7	2.60	2.60	1.42	29.72
	3.7		2.70			
	3.5		2.50			
3	3.7	3.76	2.80	2.73	1.37	27.39
	3.7		2.70			
	3.9		2.70			
4	3.8	3.83	2.8	2.83	1.35	26.10
	3.8		2.8			
	3.9		2.9			
5	3.9	3.9	3.1	2.96	1.31	24.10
	3.9		2.9			
	3.9		2.9			

4.1.8 Angle of Repose Measurement for the ratios of Amlodipine set-1

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

4.8 Table: Calculation of Angle of repose for Amlodipine set-1

Ratio	Height (h) cm	Avg. Height (h) cm	Radius (r) cm	Average Radius (r) cm	Angle of Repose(^{0})
Ratio 1	1.2	1.24	2.5	2.30	28.33
	1.3		2.3		
	1.3		2.4		
	1.2		2.2		
	1.2		2.1		
Ratio 2	1.2	1.26	2.5	2.54	26.38
	1.2		2.6		
	1.3		2.5		
	1.4		2.4		
	1.2		2.7		
Ratio 3	1.1	1.20	2.5	2.52	24.46
	1.2		2.4		
	1.3		2.5		
	1.2		2.6		
	1.2		2.6		
Ratio 4	1.2	1.18	2.7	2.66	23.92
	1.2		2.6		
	1.1		2.6		
	1.3		2.8		
	1.1		2.6		
Ratio 5	1.1	1.16	2.9	2.82	22.35
	1.3		2.8		
	1.1		2.9		
	1.1		2.7		
	1.2		2.8		

4.1.9 Results of the ratios of amlodipine set-2

For calculating Carr's index and Hausner ratio for the mixed quantity of amlodipine and formula-2, their individual bulk volume and tapped volume were measured five times and the average value was taken. The observed value is given below

Table 4.9: Calculation of Carr's index and Hausner ratio for amlodipine set-2

Ratio	Bulk Volume, V_1 (ml)	Most Acceptable Value of V_o(ml)	Tapped Volume, V2 (ml)	Most Acceptable value of V_r(ml)	Hausner 's Ratio V_0/V_r	Compressibility index $100\times(V_0-V_r)/V_0$
Ratio 1	3.5 3.2 3.1	3.26	2.1 2.5 2.2	2.26	1.44	30.67
Ratio 2	3.5 3.1 3.3	3.30	2.2 2.3 2.5	2.33	1.41	29.39
Ratio 3	3.4 3.4 3.3	3.36	2.3 2.5 2.5	2.43	1.38	27.67
Ratio 4	3.3 3.5 3.4	3.40	2.5 2.5 2.5	2.5	1.36	26.47
Ratio 5	3.5 3.3 3.6	3.46	2.7 2.5 2.6	2.6	1.33	24.85

4.1.10 Angle of Repose measurement for the ratios of amlodipine set-2

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

4.10 Table: Calculation of Angle of repose for amlodipine set-2

Ratio	Height (h) cm	Avg. Height (h) cm	Radius (r) cm	Average Radius (r) cm	Angle of Repose(^{0})
Ratio 1	1.2	1.28	2.3	2.24	29.74
	1.2		2.5		
	1.3		2.1		
	1.4		2.2		
	1.3		2.1		
Ratio 2	1.3	1.24	2.6	2.36	27.71
	1.2		2.4		
	1.2		2.4		
	1.4		2.2		
	1.1		2.2		
Ratio 3	1.2	1.24	2.5	2.38	27.51
	1.2		2.3		
	1.3		2.5		
	1.2		2.2		
	1.3		2.4		
Ratio 4	1.3	1.22	2.5	2.44	26.56
	1.2		2.3		
	1.1		2.6		
	1.3		2.5		
	1.2		2.3		
Ratio 5	1.1	1.18	2.3	2.48	25.44
	1.1		2.7		
	1.2		2.5		
	1.3		2.4		
	1.2		2.5		

4.1.11 Results of the ratios of amlodipine set-3

For calculating Carr's index and Hausner ratio for the mixed quantity of amlodipine and set-3, their individual bulk volume and tapped volume were measured five times and the average value was taken. The observed value is given below

Table 4.11: Calculation of Carr's index and Hausner ratio for amlodipine set-3

Ratio	Bulk Volume, V_1 (ml)	Most Acceptable Value of V_o(ml)	Tapped Volume, V2 (ml)	Most Acceptable value of V_r(ml)	Hausner's Ratio V_0/V_r	Compressibility index $100\times(V_0-V_r)/V_0$
Ratio 1	3.4	3.46	2.2	2.23	1.55	35.54
	3.2		2.3			
	3.5		2.2			
Ratio 2	3.4	3.36	2.3	2.27	1.48	32.44
	3.3		2.2			
	3.4		2.3			
Ratio 3	3.2	3.20	2.4	2.36	1.35	26.25
	3.3		2.4			
	3.1		2.3			
Ratio 4	3.0	3.03	2.3	2.40	1.26	19.10
	3.1		2.5			
	3.0		2.4			
Ratio 5	3.0	2.94	2.5	2.53	1.16	13.95
	2.8		2.6			
	3.0		2.5			

4.1.12 Angle of Repose measurement for the ratios of amlodipine set-3

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

4.12 Table: Calculation of Angle of repose for Amlodipine set-3

Ratio	Height (h) cm	Avg. Height (h) cm	Radius (r) cm	Average Radius (r) cm	Angle of Repose (^{0})
Ratio 1	1.4	1.42	2.1	2.16	33.32
	1.5		2.3		
	1.5		2.2		
	1.3		2.1		
	1.4		2.1		
Ratio 2	1.3	1.32	2.4	2.24	30.51
	1.3		2.1		
	1.3		2.1		
	1.4		2.3		
	1.3		2.3		
Ratio 3	1.3	1.24	2.6	2.38	27.51
	1.3		2.3		
	1.1		2.1		
	1.3		2.4		
	1.2		2.5		
Ratio 4	1.2	1.14	2.5	2.48	24.68
	1.1		2.3		
	1.1		2.6		
	1.2		2.4		
	1.1		2.6		
Ratio 5	1.1	1.02	2.7	2.58	21.57
	1.0		2.5		
	1.1		2.5		
	0.8		2.6		
	1.1		2.6		

4.1.13 Results of the ratios of propranolol set-1

For calculating Carr's index and Hausner ratio for the mixed quantity of Propranolol and set-1, their individual bulk volume and tapped volume were measured five times and the average value was taken. The observed value is given below

Table 4.13: Calculation of Carr's index and Hausner ratio for propranolol set-1

Ratio	Bulk Volume, V_1 (ml)	Most Acceptable Value of V_o(ml)	Tapped Volume, V2 (ml)	Most Acceptable value of V_r(ml)	Hausner's Ratio V_0/V_r	Compressibility index $100\times(V_0-V_r)/V_0$
Ratio 1	3.5	3.66	2.50	2.36	1.55	35.51
	3.7		2.30			
	3.8		2.30			
Ratio 2	3.8	3.70	2.30	2.40	1.54	35.13
	3.5		2.50			
	3.8		2.40			
Ratio 3	3.7	3.73	2.50	2.60	1.43	30.29
	3.7		2.80			
	3.8		2.50			
Ratio 4	3.8	3.76	3.00	2.83	1.33	24.73
	3.6		3.00			
	3.9		2.50			
Ratio 5	3.8	3.83	3.00	2.93	1.30	23.50
	3.8		2.90			
	3.9		2.90			

4.1.14 Angle of Repose measurement for the ratios of propranolol set-1

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

4.14 Table: Calculation of Angle of repose for propranolol set-1

Ratio	Height (h) cm	Avg. Height (h) cm	Radius (r) cm	Average Radius (r) cm	Angle of Repose (^{0})
Ratio 1	1.2	1.30	1.9	2.12	31.58
	1.3		2.1		
	1.3		2.2		
	1.4		2.1		
	1.3		2.3		
Ratio 2	1.2	1.26	2.1	2.18	30.02
	1.2		2.2		
	1.3		2.1		
	1.3		2.3		
	1.3		2.2		
Ratio 3	1.1	1.22	2.3	2.30	27.94
	1.2		2.1		
	1.3		2.3		
	1.3		2.5		
	1.2		2.3		
Ratio 4	1.1	1.22	2.3	2.34	27.53
	1.2		2.1		
	1.2		2.4		
	1.4		2.4		
	1.2		2.5		
Ratio 5	1.1	1.18	2.5	2.42	25.99
	1.3		2.5		
	1.3		2.3		
	1.1		2.3		
	1.1		2.4		

4.1.15 Results of the ratios of propranolol set-2

For calculating Carr's index and Hausner ratio for the mixed quantity of Propranolol and set-2, their individual bulk volume and tapped volume were measured five times and the average value was taken. The observed value is given below

Table 4.15: Calculation of Carr's index and Hausner ratio for Propranolol set-2

Ratio	Bulk Volume, V_1 (ml)	Most Acceptable Value of V_o(ml)	Tapped Volume, V2 (ml)	Most Acceptable value of V_r(ml)	Hausner's Ratio V_0/V_r	Compressibility index $100\times(V_0-V_r)/V_0$
Ratio 1	3.40	3.40	2.10	2.23	1.52	34.41
	3.30		2.30			
	3.50		2.30			
Ratio 2	3.60	3.40	2.20	2.27	1.49	33.23
	3.30		2.30			
	3.30		2.30			
Ratio 3	3.20	3.43	2.40	2.37	1.44	30.90
	3.60		2.30			
	3.50		2.40			
Ratio 4	3.60	3.47	2.40	2.43	1.42	28.90
	3.50		2.50			
	3.30		2.40			
Ratio 5	3.50	3.50	2.7	2.53	1.38	27.71
	3.50		2.5			
	3.50		2.4			

4.1.16 Angle of Repose measurement for the ratios of propranolol set-2

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

4.16 Table: Calculation of Angle of repose for propranolol formula 2

Ratio	Height (h) cm	Avg. Height (h) cm	Radius (r) cm	Average Radius (r) cm	Angle of Repose (^{0})
Ratio 1	1.40	1.36	1.90	1.98	34.48
	1.30		2.1		
	1.40		2.0		
	1.40		2.1		
	1.30		1.8		
Ratio 2	1.40	1.32	2.1	2.10	32.15
	1.30		2.2		
	1.30		1.9		
	1.30		2.2		
	1.30		2.1		
Ratio 3	1.30	1.26	1.8	2.10	30.96
	1.30		1.9		
	1.20		2.3		
	1.20		2.2		
	1.30		2.3		
Ratio 4	1.20	1.23	2.3	2.16	29.65
	1.20		2.2		
	1.30		2.1		
	1.30		2.2		
	1.20		2.0		
Ratio 5	1.10	1.18	2.3.	2.20	28.20
	1.20		2.0		
	1.10		2.3		
	1.30		2.1		
	1.20		2.3		

4.1.17 Results of the ratios of propranolol set-3

For calculating Carr's index and Hausner ratio for the mixed quantity of Propranolol and set-3, their individual bulk volume and tapped volume were measured five times and the average value was taken. The observed value is given below

Table 4.17: Calculation of Carr's index and Hausner ratio for propranolol set-3

Ratio	Bulk Volume, V_1 (ml)	Most Acceptable Value of V_o(ml)	Tapped Volume, V2 (ml)	Most Acceptable value of V_r(ml)	Hausner's Ratio V_0/V_r	Compressibility index $100\times(V_0-V_r)/V_0$
Ratio 1	3.5	3.53	2.30	2.26	1.56	35.98
	3.5		2.50			
	3.6		2.30			
Ratio 2	3.5	3.50	2.5	2.50	1.40	28.57
	3.6		2.4			
	3.4		2.6			
Ratio 3	3.5	3.43	2.7	2.67	1.28	22.15
	3.2		2.6			
	3.6		2.7			
Ratio 4	3.1	3.23	2.8	2.73	1.18	15.47
	3.3		2.7			
	3.3		2.7			
Ratio 5	3.1	3.00	2.8	2.76	1.09	8.00
	3.0		2.7			
	2.9		2.8			

4.1.18 Angle of Repose measurement for the ratios of propranolol set-3

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

Table 4.18: Calculation of Angle of repose for propranolol set-3

Ratio	Height (h) cm	Avg. Height (h) cm	Radius (r) cm	Average Radius (r) cm	Angle of Repose (^{0})
Ratio 1	1.2	1.22	2.1	2.02	31.13
	1.2		2.0		
	1.2		2.0		
	1.3		1.9		
	1.2		2.1		
Ratio 2	1.2	1.14	2.1	2.02	27.39
	1.1		1.9		
	1.2		2.1		
	1.1		2.1		
	1.1		1.9		
Ratio 3	0.9	1.04	2.1	2.14	25.91
	1.1		2.3		
	1.2		2.0		
	1.1		2.1		
	0.9		2.2		
Ratio 4	1.0	1.00	2.5	2.30	23.49
	1.1		2.3		
	1.0		2.3		
	1.1		2.1		
	0.8		2.3		
Ratio 5	1.1	0.96	2.3	2.40	21.80
	1.2		2.2		
	0.7		2.5		
	1.1		2.8		
	0.7		2.2		

4.2 COMPARISON

Comparison shown using graph among 3 types (excipients, amlodipine, propranolol) of formulations (f1, f2, f3,) on the basis of Carr's index, Hausner ratio, and Angle of repose

4.2.1 Carr's Index

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

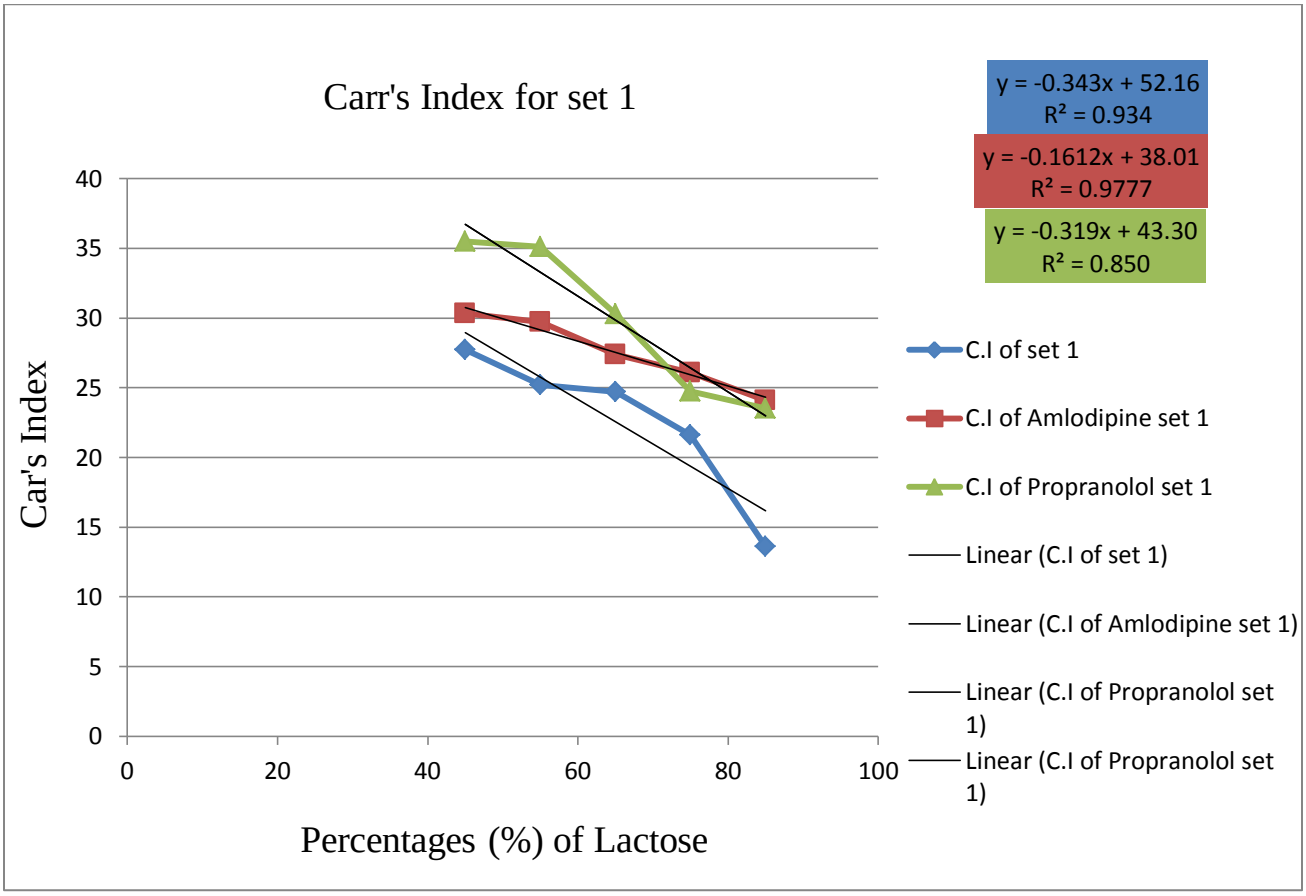


Figure 4.1: A percentage ratio of Lactose versus Carr's Index graph

4.2.2 Hausner's Ratio

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

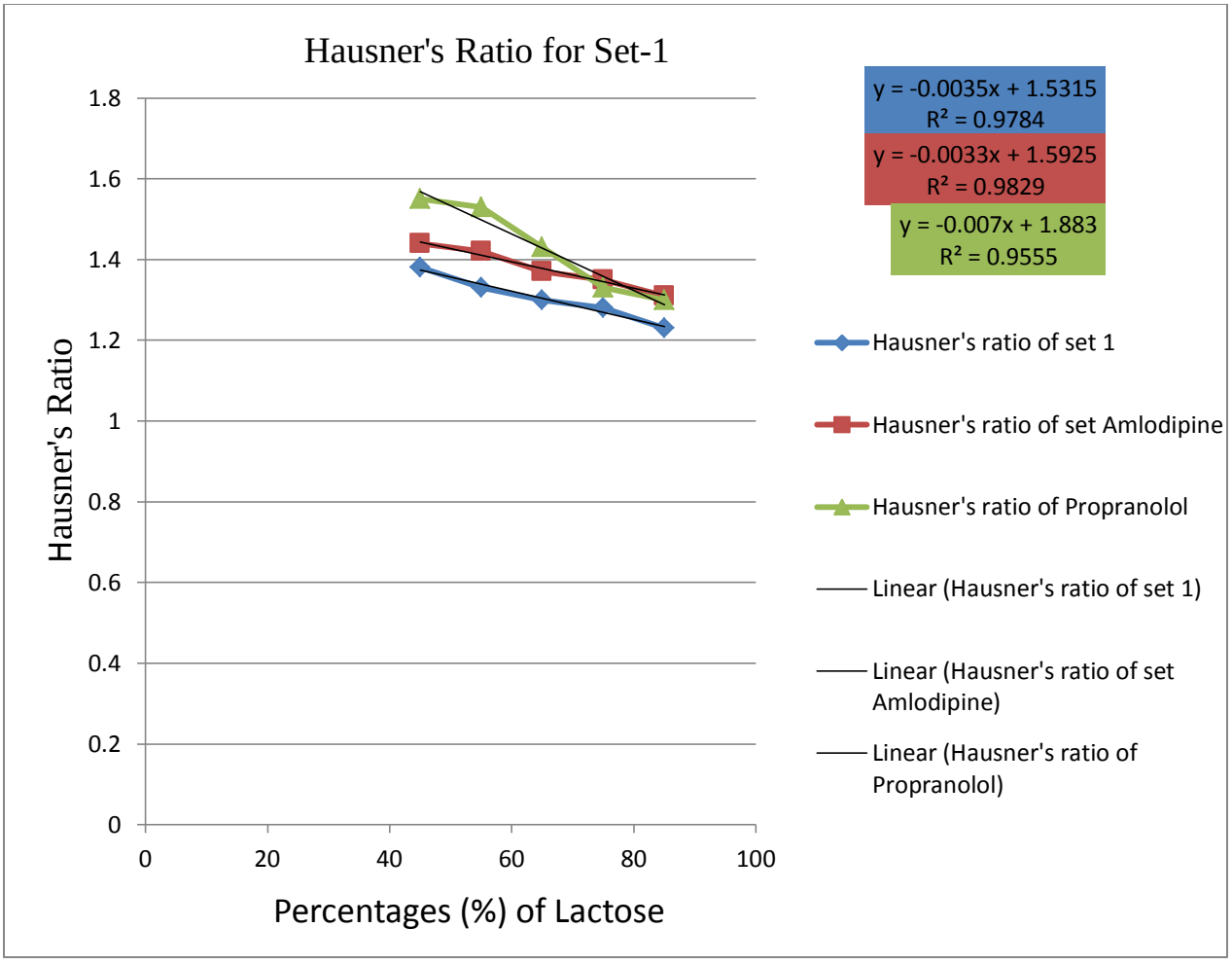


Figure 4.2: A percentage ratio of Lactose versus Hausner's ratio graph

4.2.3 Angle of repose

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

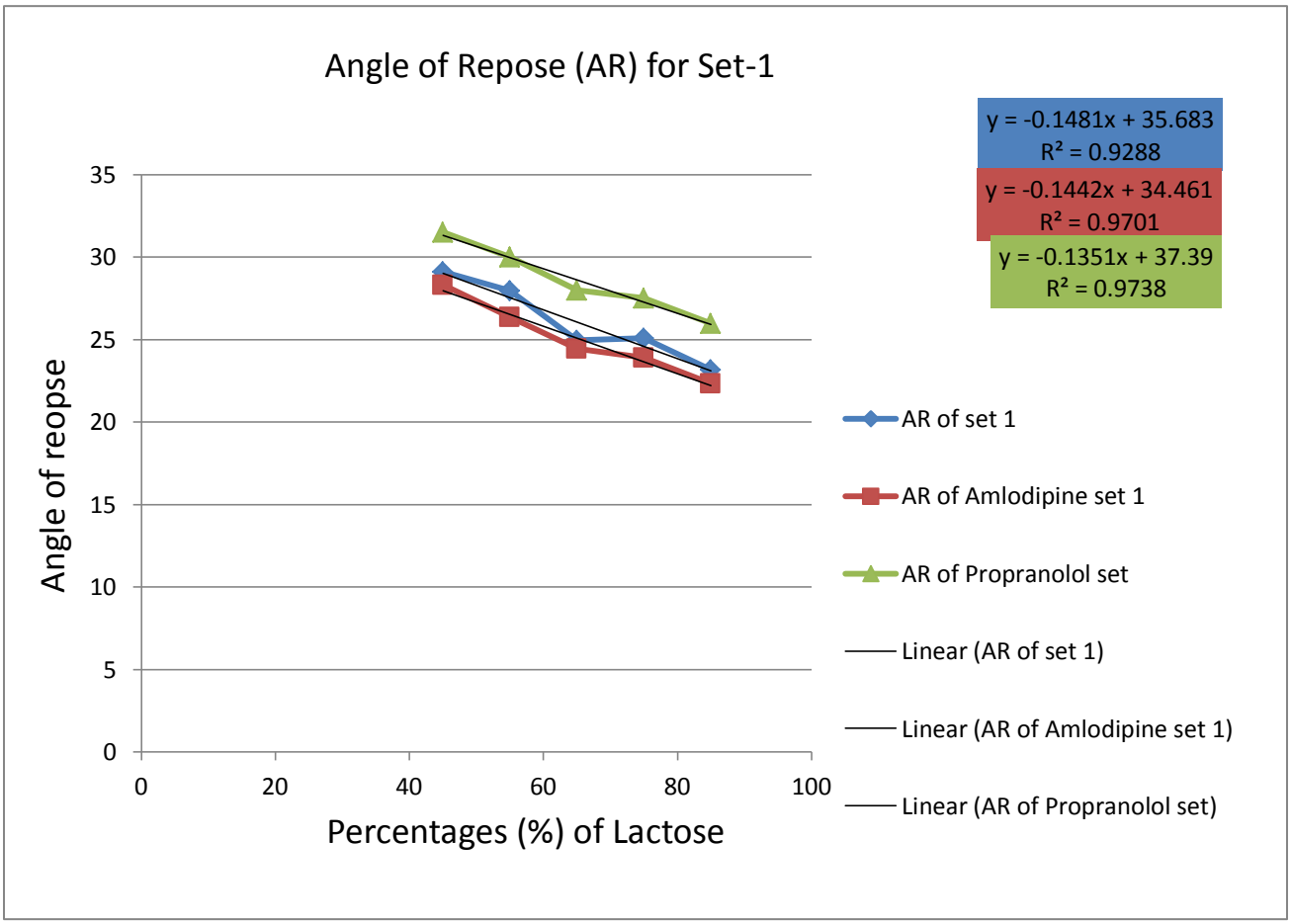


Figure 4.3: A percentage ratio of Lactose versus Angle of Repose (AR) graph.

4.2.4 Carr's Index

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

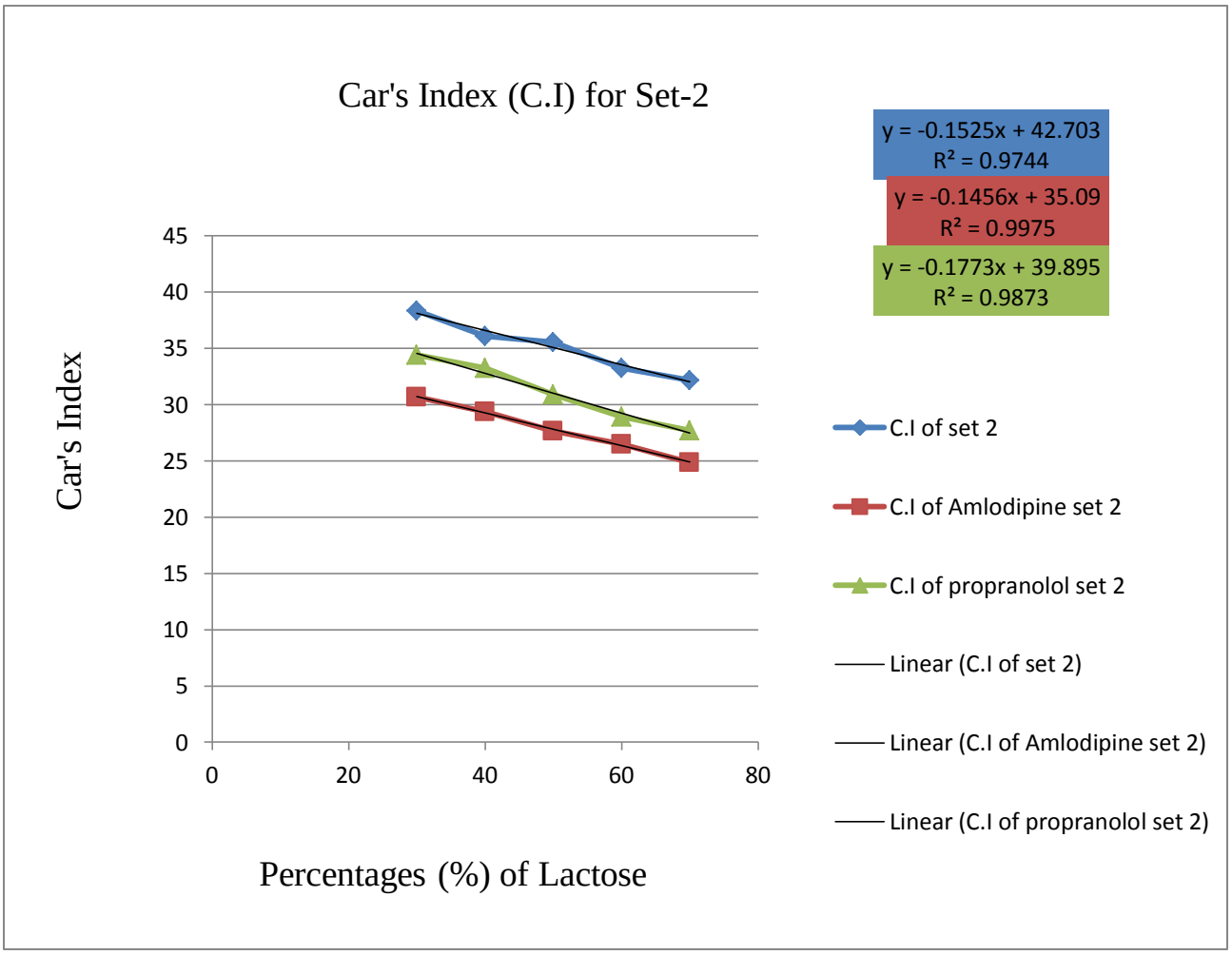


Figure 4.4: A percentage ratio of Lactose versus Carr's Index graph

4.2.5 Hausner's Ratio

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

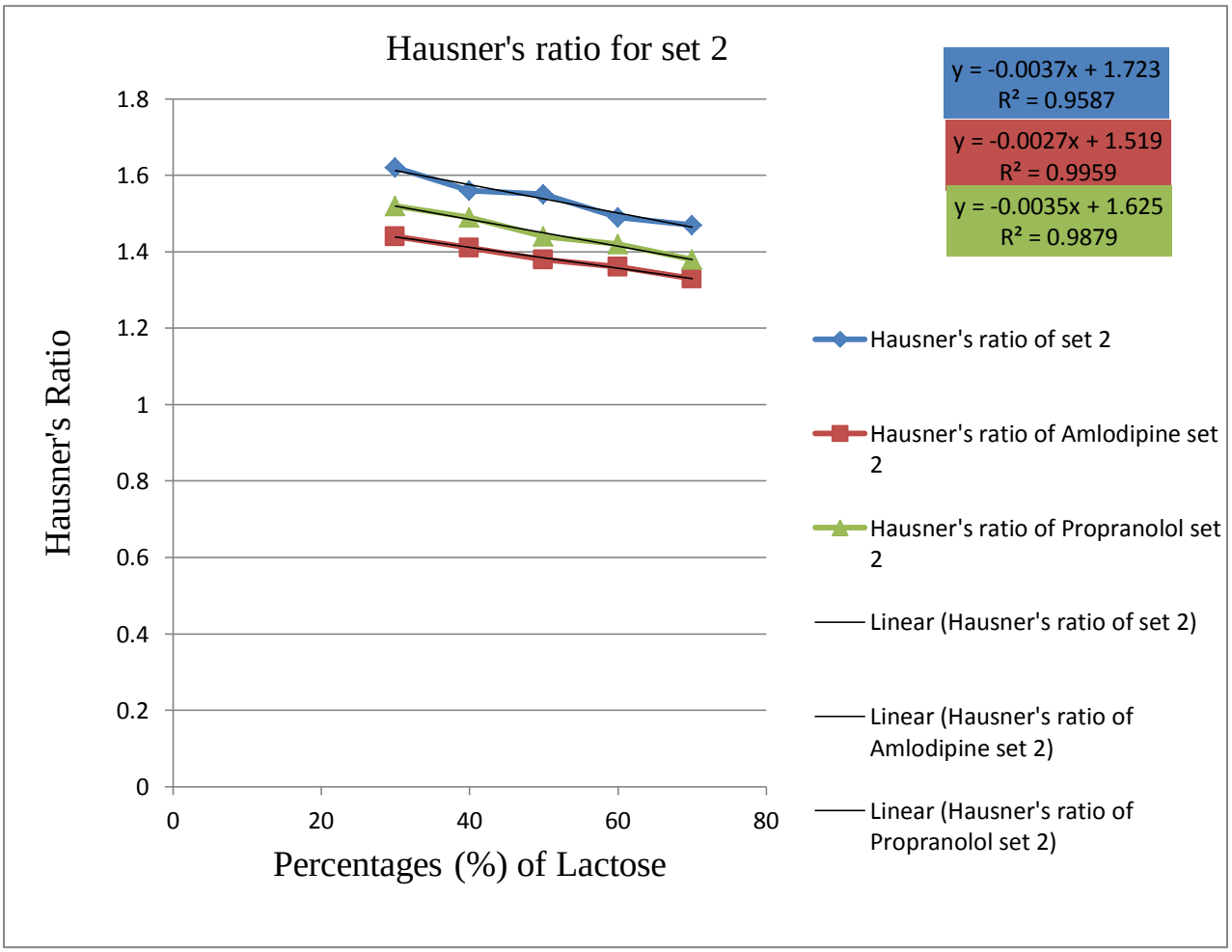


Figure 4.5: A percentage ratio of Lactose versus Hausner's ratio graph

4.2.6 Angle of repose

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

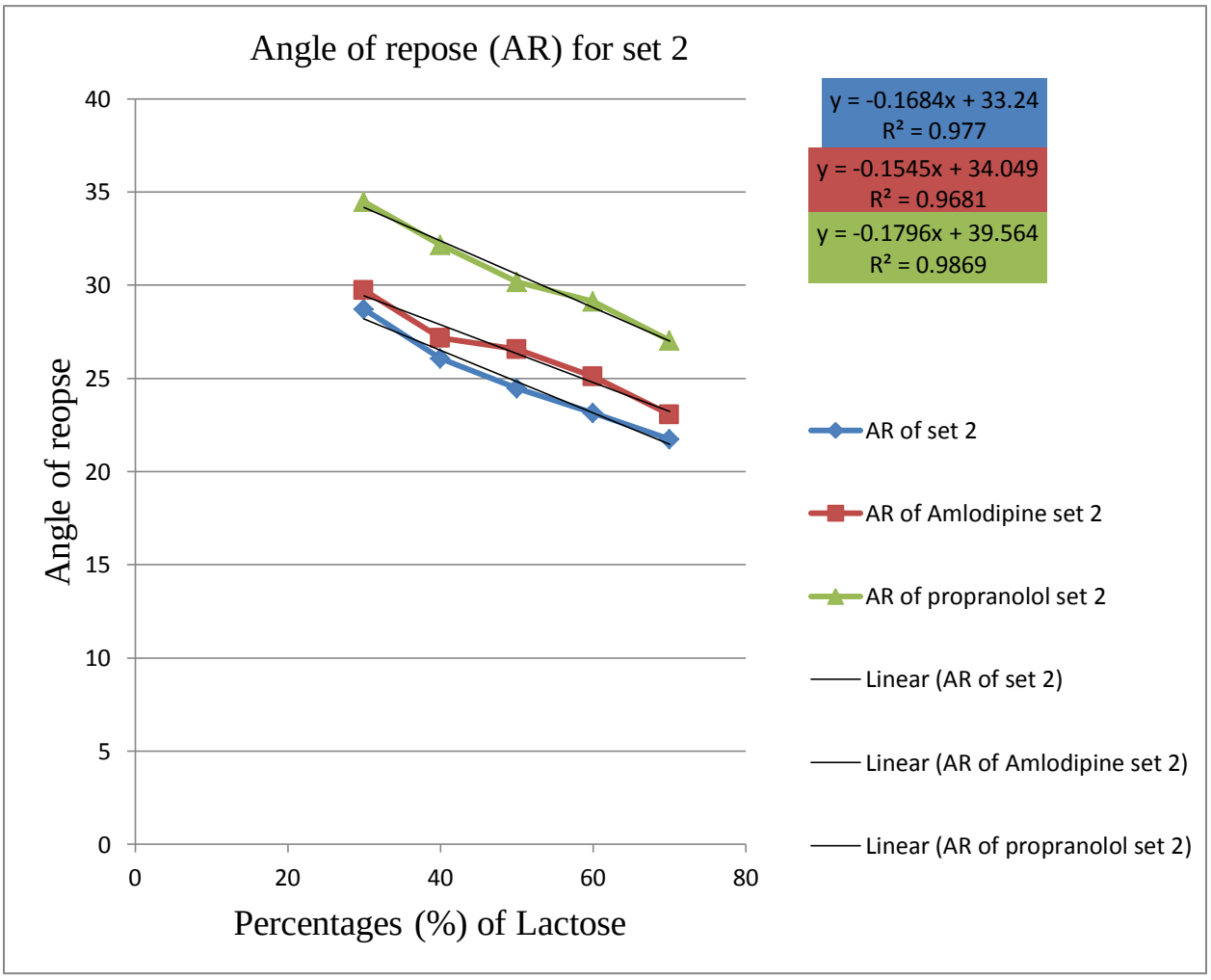


Figure 4.6: A percentage ratio of Lactose versus Angle of Repose (AR) graph.

4.2.7 Car's Index

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

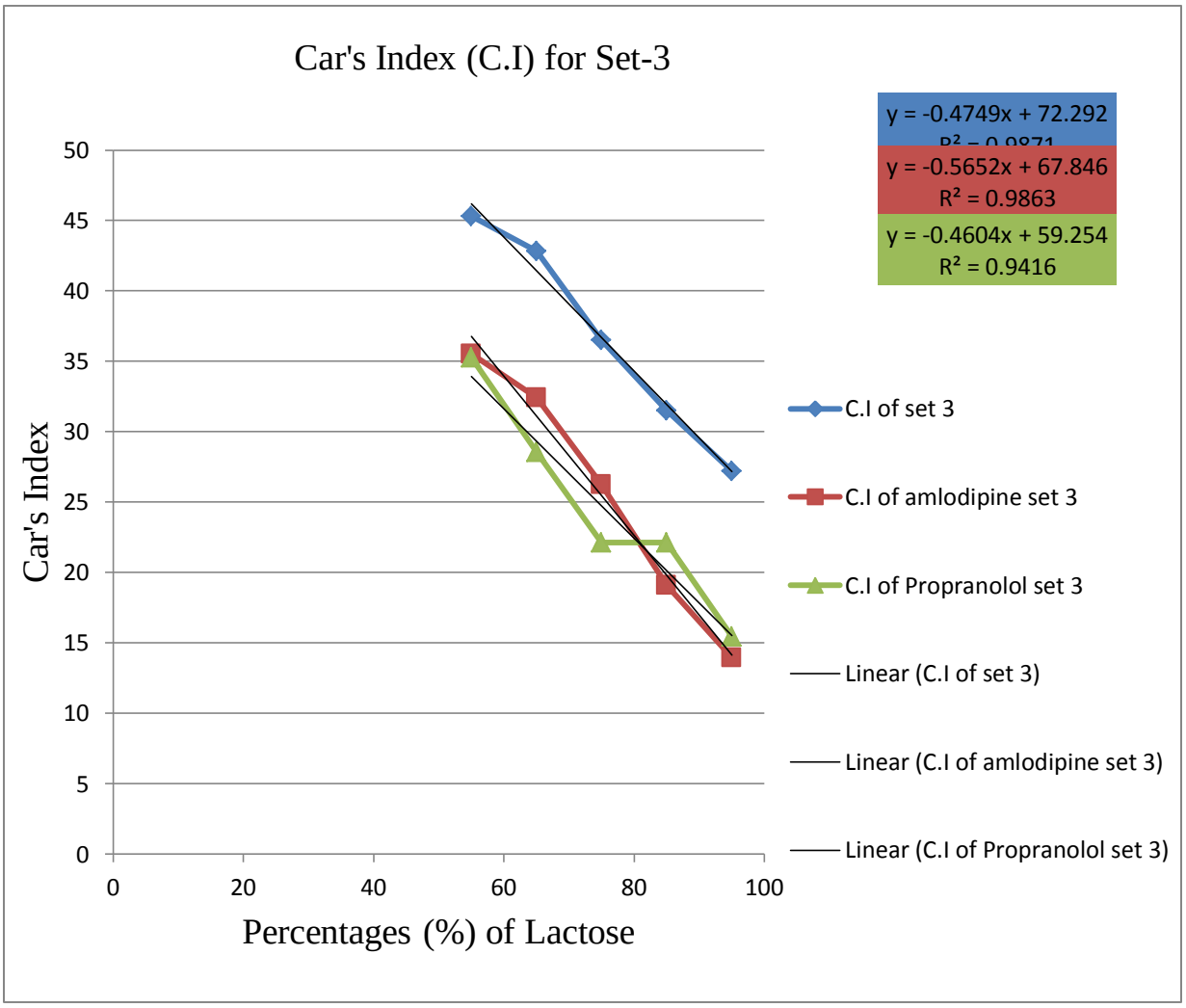


Figure 4.7: A percentage ratio of Lactose versus Carr's Index graph

4.2.8 Hausner's ratio

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

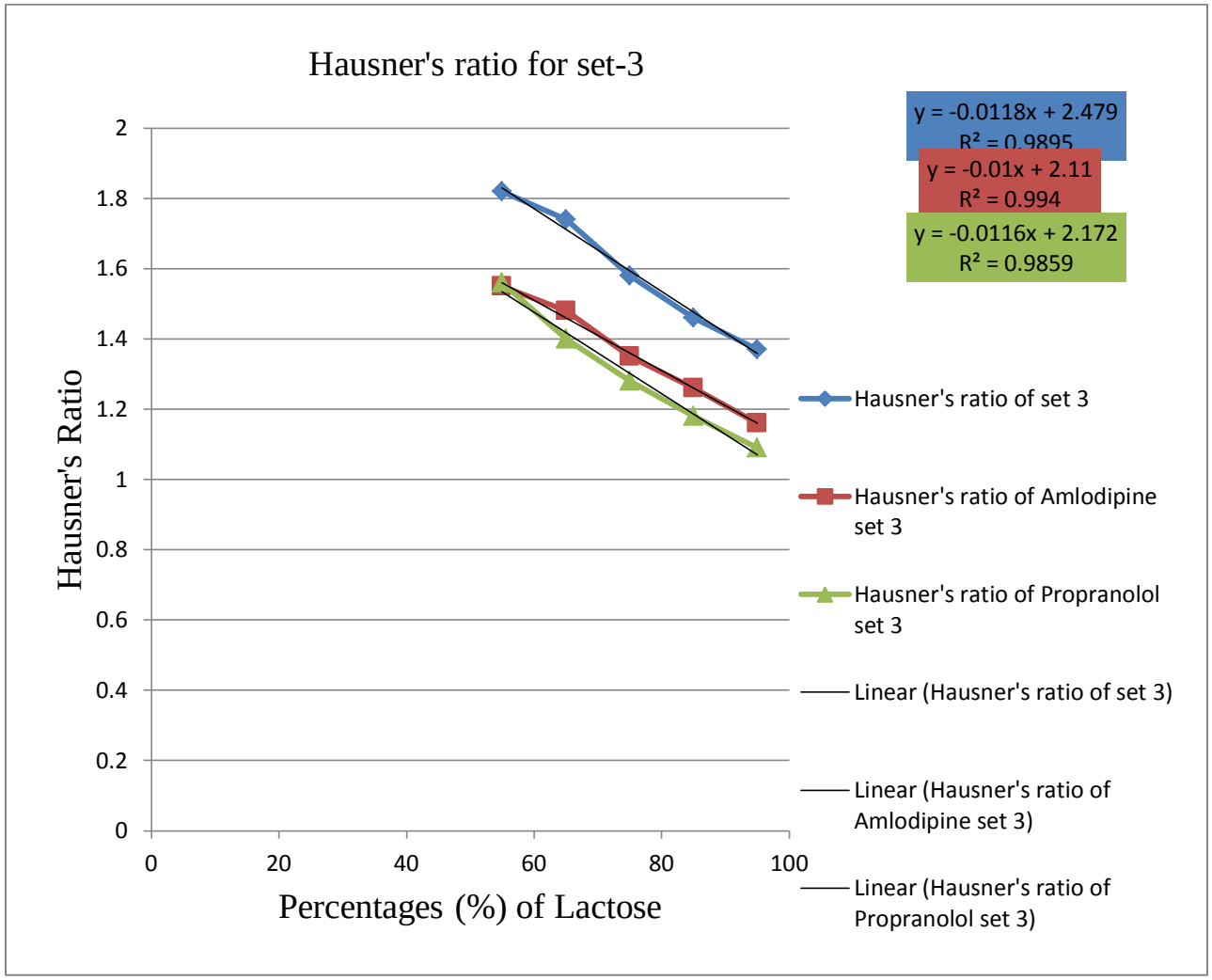


Fig 4.8: A percentage ratio of Lactose versus Hausner's ratio graph

4.2.9 Angle of repose

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

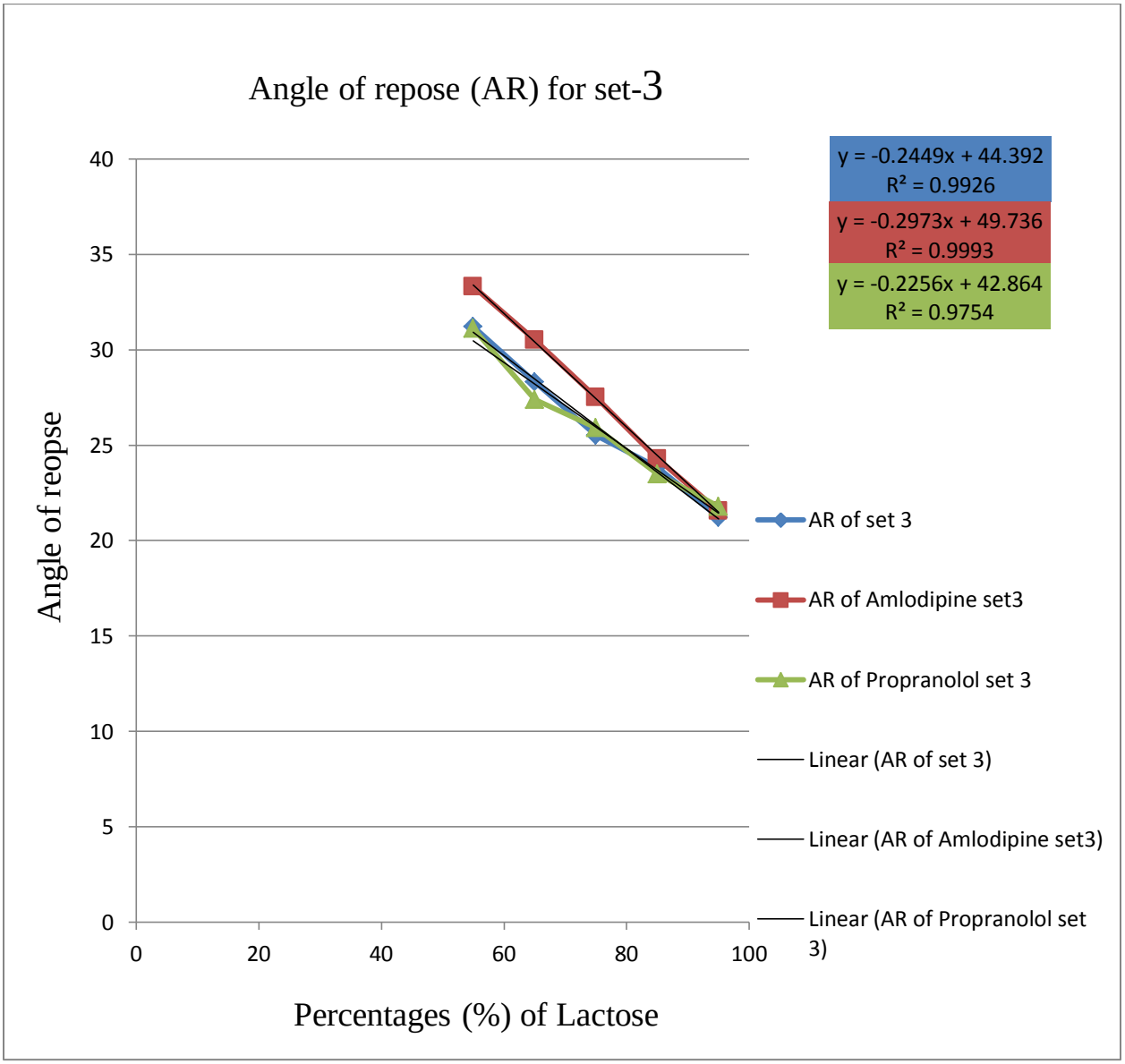


Figure 4.9: A percentage ratio of Lactose versus Angle of Repose (AR) graph.

4.3 Equation and regression value of graph

Table 4.19: Equation and regression value for Carr's index

Carr's Index	Equation and Regression value
Set-1	y = -0.343x + 52.16 R^2 = 0.934…(i)
Set-2	y = -0.152x + 42.70 R^2 = 0.974…(ii)
Set-3	y = -0.474x + 72.29 R^2 = 0.987....(iii)
Amlodipine with set-1	y = -0.161x + 38.01 R^2 = 0.977….(iv)
Amlodipine with set-2	y = -0.145x + 35.09 R^2 = 0.997…(v)
Amlodipine with set-3	y = -0.565x + 67.84 R^2 = 0.986…(vi)
Propranolol with set-1	y = -0.319x + 43.30 R^2 = 0.850….(vii)
Propranolol with set-2	y = -0.177x + 39.89 R^2 = 0.987….(viii)
Propranolol with set-3	y = -0.460x + 59.25 R^2 = 0.941….(ix)

Table 4.20: Equation and regression value for Hausner's ratio

Hausner's Ratio	Equation and Regression value
Set-1	y = -0.003x + 1.531 R^2 = 0.978….(i)
Set-2	y = -0.003x + 1.723 R^2 = 0.958….(ii)
Set-3	y = -0.011x + 2.479 R^2 = 0.989….(iii)
Amlodipine with set-1	y = -0.161x + 38.01 R^2 = 0.977….(iv)
Amlodipine with set-2	y = -0.002x + 1.519 R^2 = 0.995…..(v)
Amlodipine with set-3	y = -0.01x + 2.11 R^2 = 0.994……(vi)
Propranolol with set-1	y = -0.319x + 43.30 R^2 = 0.850….(vii)
Propranolol with set-2	y = -0.003x + 1.625 R^2 = 0.987….(viii)
Propranolol with set-3	y = -0.011x + 2.172 R^2 = 0.985….(ix)

Table 4.21: Equation and regression value for Angle of Repose

Angle of Repose	Equation and Regression value
Set-1	$y = -0.148x + 37.16$ $R^2 = 0.928$….(i)
Set-2	$y = -0.168x + 33.24$ $R^2 = 0.977$….(ii)
Set-3	$y = -0.244x + 44.39$ $R^2 = 0.992$….(iii)
Amlodipine with set-1	$y = -0.144x + 35.90$ $R^2 = 0.970$ ….(iv)
Amlodipine with set-2	$y = -0.154x + 34.04$ $R^2 = 0.968$….(v)
Amlodipine with set-3	$y = -0.297x + 49.73$ $R^2 = 0.999$….(vi)
Propranolol with set-1	$y = -0.136x + 38.86$ $R^2 = 0.968$….(vii)
Propranolol with set-2	$y = -0.179x + 39.56$ $R^2 = 0.986$….(viii)
Propranolol with set-3	$y = -0.225x + 42.86$ $R^2 = 0.975$….(ix)

Chapter-V

Discussion

5.1 DISCUSSION

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

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

  Flow property of different formulas can be easily understood from the table 4.6 for hausner's ratio. From these equations we can find out any desired flow property. For example, if we consider equation (I) $y = -0.148x + 37.16$ $R^2 = 0.928$; here Y value represents percentage of Lactose. For any percentage of Lactose the value for X can be determined with desired R value. Most desirable regression value determined for excipient formula for set-3 (equation iii: $y = -0.244x + 44.39$ $R^2 = 0.992$) and for

amlodipine and propranolol for set-2 (equation v: $y = -0.154x + 34.04$ $R^2 = 0.968$ and viii: $y = -0.179x + 39.56$ $R^2 = 0.986$).

- In case of formula 2 (table 4.3), the most desirable result was observed for 60%:30% (Lactose: Formula 2) ratio. For this ratio the range for hausner's ratio and carr's index was in fair range but angle of repose was changed to excellent range. Here the percentage for binder was same in formulation which might be a reason for poor result. As human error was less in this case of formula 2. Here also the flow ability increases with increasing degree of diluent. The values of amlodipine and propranolol were similar to the excipient values. When the results were plotted into straight line equation all three formulation showed a good result. The result from the equation for both amlodipine and propranolol were increased than the excipient formulation equation.

- In case of formula 3, it showed better results than above two for hausner's ratio, carr's index and angle of repose (table 4.5, 4.6, 4.11, 4.12, 4.17 and 4.18). The reason behind this might be the ratio of the excipient used. Here percentage of binder was reduced than above two formulas. In formula 3 the amount of lactose was less, if they were used in higher amount the result might be improved from fair to good as flow properties are increased with increasing degree of Lactose. All the parameters were in good range for this ratio. When compared in straight line equation propranolol showed better value than amlodipine but both APIs flow property slightly improved from the excipient formulation.

Chapter-VI

Conclusion

6.1 Conclusion

The flow of powder during manufacturing indicates the quality of product. Flow of powder also affects the manufacturing efficiency. During formulation development the flow of blend may affects the exicipients selection and determine whether the direct compression method can be used or not. So the knowledge of flow property of pharmaceutical solid dosage forms is very important for the pharmaceutical industries. Improved or faster flowability will increase the production of solid dosage forms. As excipient are used as a major portion of a solid dosage form. This experiment was done to find out several equations for various ratios of Lactose used. These equations will help the future researchers and pharmaceutical personnel to predict and determine the flowability of mixtures for adding the Lacrose. For further research projects on powder mixture flow property and new formulation determination, this research will help to save money and time.

Chapter-VI

References

7.1 References

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