Determination of Variation in Flow Property of Different Formulas of Calcium phosphate 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.

CERTIFICATE BY THE SUPERVISOR

This is to certify that the dissertation entitled **"Determination of variation in flow property of different formulas of Ca phosphate along with Amlodipine and Propranolol"** submitted to the Department of Pharmacy, East West University, in partial fulfillment of the requirements for the Degree of Bachelor of Pharmacy, was carried out by **Umme Habiba**, **ID No. 2012-1-70-031** under my supervision and no part of this dissertation has been or is being submitted elsewhere for the award of any Degree/Diploma.

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ENDORSEMENT BY THE CHAIRPERSON

This is to certify that the dissertation entitled **"Determination of variation in flow property of different formulas of Ca phosphate along with Amlodipine and Propranolol"** is a genuine research work carried out by **Umme Habiba**, under the supervision of **Mr. Md. Anisur Rahman,** Senior Lecturer (supervisor) and **Mr. Mohammed Faisal Bin Karim,** Senior Lecturer (co supervisor) from 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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DECLARATION BY THE CANDIDATE

I, **Umme Habiba**, hereby declare that this dissertation, entitled "**Determination of variation in flow property of different formulas of Ca phosphate along with Amlodipine and Propranolol**" is an authentic and genuine thesis project carried out by me under the guidance of and **Mr. Md. Anisur Rahman,** Senior Lecturer, (supervisor), **Mr. Mohammed Faisal Bin Karim,** Senior Lecturer, (co supervisor) Department of Pharmacy, East West University, Dhaka.

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Umme Habiba

Dedication

This Research Paper is dedicated

To

My Beloved Parents

ABSTRACT

This work was proposed to determine the flow properties of different set of some important pharmaceutical excipients along with APIs that are most commonly used to search some equations which can predict the flow property of any set of excipients and APIs with different ratio of diluent. Different parameters to determine flow property such as Compressibility index, Hausner ratio, and angle of repose were observed for them. Many unique formulas were equipped by choosing various excipients from different classes. Diluents were mixed with these prepared formulas in different specific and justified ratio. The prepared mixture in a constant weight was then examined for measuring flow property. I also used APIs to determine the difference in flow property. The values of Carr's index, Hausner ratio and angle of repose were plotted against the percentage ratios of diluent. The study showed a linear relationship with different ratios of mixture and flow property measuring parameters. From these graphs the straight-line equations for each set of formula were obtained with regression value close to 1 which can be used to predict the flow property of these formula with different ratio of diluents. Moreover the most suitable ratio of specific diluent and a specific set of excipients along with APIs were proposed that showed better flow property.

Key words: Carr's Index, Hausner Ratio, Angle of repose, bulk volume, tapped volume, diluent.

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Chapter One

INTRODUCTION

1.1 Introduction (Young, 2013)

Medicines are available in many dosage forms including tablets, capsules, oral liquids, topical creams and gels, transdermal patches, injectable products, implants, eye products, nasal products, inhalers and suppositories. Pharmaceutical excipients are substances that are included in a pharmaceutical dosage form not for their direct therapeutic action, but to aid the manufacturing process, to protect, support or enhance stability, or for bioavailability or patient acceptability. Their flow property influences the other most important factors of tablet or capsule dosage forms (such as, disintegration, dissolution, stability etc.) which determines the efficacy of that dosage form at the site of action. They may also assist in product identification and enhance the overall safety or function of the product during storage or use.

The objective of this research project is to identify the nature of flow of a particular formulation prepared only by various powdered excipients with different amount of diluents. This experiment may turn out of great importance as there are many drug formulations in which powdered excipients are used, for example, in case of powder for suspension, tablets, capsule, even in semisolid preparations (gel, cream, ointment etc.) and suppositories to some extent. Surprisingly, soluble powdered excipients are also used in liquid preparations, like syrup and solutions. In my study I have chosen to compare the flow properties of a group of excipients while adding different amount of diluent with it. The main purpose of this research work is to determine, whether changing amount of diluent changes the flow property of a group of excipients or not. If they really change, to what extent the changes occur and the changes result in good or bad impact for the whole formulation.

It has been anticipated that powders account for 80% of materials used in industry. Handling and processing powders, particulates and granules is essential to the pharmaceutical industry, but has traditionally been fraught with problems due to their unpredictable and irregular behavior, specifically with respect to flow ability. With so many raw materials, semi-finished and finished products in powder form, pharmaceutical companies stand to increase significant manufacturing and commercial profits from improvements in the evaluation of powder flow. Powder flow analysis is really valuable in the pharmaceutical industry, as well as in several others. Objective and repeatable testing combined with ranking of dry powder samples can provide significant opportunities and benefits. These contain optimizing batch and source selection in terms of cost

and quality; the progress of best mix formulations; optimizing scaling up and process conditions; and maintaining product quality control. Innovative technology provides such data either by measuring and comparing products capable of flow, or by assessing sample behavior under test conditions reproducing in-process or product handling conditions.

1.2 Powder Flow

1.2.1 Definition

A simple definition of powder flow ability is the ability of a powder to flow. By this definition, flow ability is sometimes thought of as a one-dimensional characteristic of a powder, whereby powders can be ranked on a sliding scale from "free-flowing" to "non-flowing". The inability to achieve reliable powder flow during manufacturing process of solid dosage forms of any drug can have a significant adverse effect on the total process, whether from manufacture tothe release of a product to market. Production costs can be significantly higher than anticipated due to interference required on the part of operators, low yield or unplanned process redesign.(Young, 2013)

1.2.2 Importance of learning accurate flow property (Slideshare, 2013)

Measuring flow rate of powders is by far one of the most important parameter to check while preparing a solid dosage form, for example, tablets, capsules, and to some extent it is also important in liquid preparations. A thorough understanding of a bulk material's flow properties and its flow characteristics are crucial for identifying the cause of poor flow, powder flooding or rate limitations, segregation, or product non-uniformity. Powder flow behavior can affect manufacturing efficiency and can directly affect product quality variables, such as dose uniformity. The critical attributes such as cohesivity index, caking strength, and flow stability are determined by examining the excipients. It is really important for a pharmaceutical manufacturer to check about the flow property of the formulation for any solid dosage form preparation. The same powder may flow well in one hopper but poorly in another; likewise, a given hopper may handle one powder well but cause another powder to hang-up. It is required to have knowledge of the flowability of any single powder or a bulk because it helps in designing powder handling equipment such as hoppers that no flow problems (flow impediments, segregation, or any irregular flow, etc.) will occur. Few methods of assessing powder flow can be time consuming.

However, the benefits of accurately exemplifying powder flow measurement can far be more important than this venture of time.

1.2.2.1 Developing new product/ dosage form

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

1.2.2.2 Quality improvement

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

1.2.2.3 Cost-savings of existing product

The substitution of expensive constituents with lower cost powders is a smart approach because the cost of existing product should be driven down. Although these substitutes may be produced to the same specification as the original substance, they may not essentially store, convey and process as effortlessly. Discovering this after production has started would incur downtime and additional cost. Final product quality may also be negotiated.

1.2.3 Factors Affecting Powder Flow Properties

Powders are probably the least predictable of all materials in relation to flowability because of the large number of factors that can change their rheological properties. Flow Properties of powders depend upon- Collective forces acting on individual particles, particle variables environmental conditions, particle size distribution, shape, cohesivity, surface texture, surface coating, particle interaction, electrostatic charge, hardness, stiffness, strength, compaction condition, humidity etc. (Slideshare, 2013)

1.3 Parameters Checked During This Experiment

Flowability of powders is multi-dimensional and in fact it depends on many powder characteristics. This is really important to know, no particular test could ever quantify flow property of powder. In fact, flowability is not an intrinsic material property at all. Flowability is the results of a combination of material physical properties that affect flow and it also vary accordingly the equipments used for handling, storing, and processing the material. Equal consideration must be given to both the material characteristics and the equipment. There are few physical parameters commonly checked while determining flow property, which have also been carried out in this experiment, and they are- Carr's index, Hausner's ratio and another important parameter named Angle of repose. Flow characteristic can also be measured by checking the powder flow through an orifice, or by shear cell method.(Copleyscientific, 2012)

1.3.1 Angle of repose

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

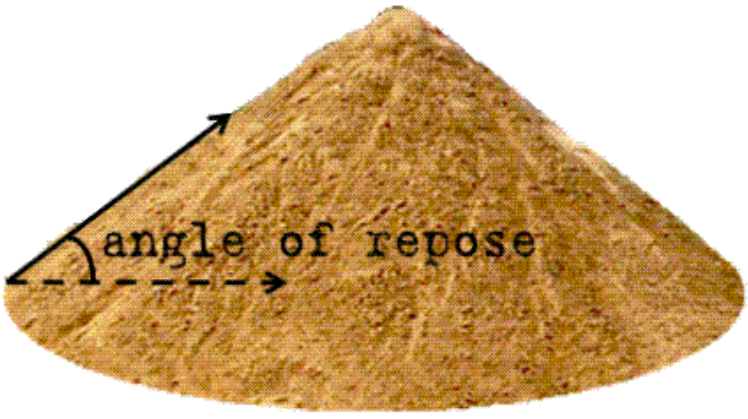


Figure 1.1: Angle of repose (Copleyscientific, 2012)

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

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

Table 1.1: Relation between flow properties and angle of repose (Copleyscientific, 2012).

Flow property	Angle of Repose
Excellent	25-30
Good	31-35
Fair-aid not needed	36-40
Passable-may hung up	41-45
Poor-must agited or vibrate	46-55
Very poor	56-65
Very, very poor	>66

There are several different methods of determining the angle of repose namely,(Copleyscientific, 2012)

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

1.3.1.2 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.

1.3.1.3 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.

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

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

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

1.3.1.4 Factors that influence the angle of repose

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

1.3.1.5 Experimental Considerations for Angle of Repose

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

• The peak of the cone of powder can be distorted by the impact of powder from above. By carefully building the powder cone, the distortion caused by impact can be minimized.

• The nature of the base upon which the powder cone is formed influences 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. (Authorstream, 2013)

1.3.1.6 Compressibility index and Hausner ratio

The two most commonly used measures of the relative importance of interparticulate interactions are the compressibility index and the Hausner ratio as these are the simplest, fast and popular methods of predicting powder flow characteristics.(Vogelpoel et al., 2004)

1.3.2 Compressibility index

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

The Carr's index is calculated by the formula below:

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

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

Where,

V_o = Bulk volume

V_f = Tapped volume

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

The compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of materials. These properties can influence the Carr's index. (Vogelpoel et al., 2004)

1.3.3 Hausner ratio

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. It is named after the engineer Henry H. Hausner. The Hausner ratio is used in a wide variety of industries as an indication of the flowability of a powder. A Hausner ratio greater than 1.25 is considered to be an indication of poor flowability and less than 1.25 is considered to be an indication of free flowing.

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

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

The inter-relation between the Angle of Repose, 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 Angle of Repose, Compressibility index (Carr's index) and Hausner ratio(Vogelpoel et al., 2004)

Flow Character	Angle of Repose	Hausner Ratio	Compressibility Index (%)
Excellent	25-30°	1.00-1.11	≤10
Good	31-35°	1.12-1.18	11-15
Fair	36-40°	1.19-1.25	16-20
Passable	41-45°	1.26-1.34	21-25
Poor	46-55°	1.35-1.45	26-31
Very Poor	56-65°	1.46-1.59	32-27
Very, Very Poor	≥66°	≥1.60	≥38

The compressibility index and Hausner ratio are determined by measuring both the bulk volume (unsettled apparent volume) and the tapped volume of the powder (after tapping the material until no further volume changes occur).(Vogelpoel et al., 2004)

1.3.4 Bulk density

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

The bulk density of a solid is often very difficult to measure since the slightest disturbance of the bed may result in a new bulk density. The interparticulate interactions that influence the bulking properties of a powder are also the interactions that interfere with powder flow.

A known weight of sample is placed into a measuring cylinder and tapped (manually or mechanically to lower the set of distance) until a consistent volume is reached which corresponds to the maximum packing density of the material. (Slideshare, 2012)

1.3.5 Tapped density

It is the maximum packing density of a powder (or blend of powders) achieved under the influence of well-defined, externally applied forces. The tapped density is obtained by mechanically tapping a graduated cylinder containing the sample until little further volume change is observed. The minimum packed volume thus achieved depends on a number of factors including particle size distribution, true density, particle shape and cohesiveness due to surface forces including moisture. Therefore, the tap density of a material can be used to predict both its flow properties and its compressibility.Tapped density is measured by tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped and volume reading was taken until little further volume change is observed. The tapping is achieved by raising the cylinder and allowing it to drop under a specified distance.

By measuring both the untapped volume and the tapped volume the following can be determined (Slideshare, 2012).

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

• True volume = the volume of powder itself

• Bulk density = mass/untapped volume

• Tapped density = mass/tapped volume

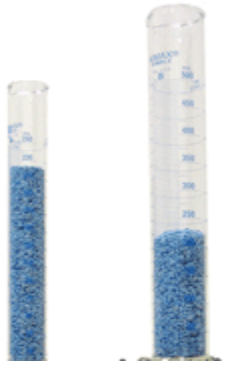


Figure 1.2: Bulk volume measurement without tapping and Tapped volume measurement after taping (Anon, 2010)

In free-flowing powders the initial bulk and tapped densities will be more similar than in poor flowing powders which yield greater differences between the two values. (Pharmacopeia, 2013)

1.3.6.1Factors that influence the bulk and tapped density

□□The diameter of the cylinder used

□□The number of times the powder is tapped to achieve the tapped density

□□The mass of material used in the test

□□Rotation of the sample during tapping (Vogelpoel et al., 2004)

1.4 Pharmaceutical Excipients

1.4.1 Definition

Excipients are defined as any substances, other than the active drug or product, that have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing of the drug delivery system during its manufacture, protect, support or enhance stability, bioavailability, or patient acceptability, assist in product identification, or enhance any other attribute of the overall safety and effectiveness of the drug delivery system during storage or use. (Anon,2010)

Drug products contain both drug substance, commonly referred to as active pharmaceutical ingredient (API) and excipients. Reasons for this include the followings:

- Ease of administration to the target patient population by the proposed route
- Improved dosing compliance
- Consistency and control of drug bioavailability
- To enable bioavailability
- Improved API stability including protection from degradation
- To ensure a robust and reproducible physical product. (Mills, 2010)

1.4.2 Types

1. Antiadherents

2. Binders

3. Coatings

4. Disintegrants

5. Fillers

6. Flavours

7. Colours

8. Lubricants

9. Glidants

10. Sorbents

11. Preservatives

12. Sweeteners

1.4.3 Antiadherent

Antiadherents 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. Most commonly used antiadherent is magnesium stearate, which is also a water soluble lubricant. Talc and starch can also be used as antiadherent. (Apu, 2010)

1.4.4. Binders

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 are usually:

□□Saccharides and their derivatives:

□□Disaccharides: sucrose, lactose;

□□Polysaccharides and their derivatives: starches, cellulose or modified cellulose such as microcrystalline cellulose and cellulose ethers such as hydroxypropyl cellulose (HPC);

□□Sugar alcohols such as xylitol, sorbitol or maltitol;

□□Protein: Gelatin

□□Synthetic polymers: polyvinylpyrrolidone (PVP), polyethylene glycol (PEG)...

□□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, starch, 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 formula. Examples include cellulose, methyl cellulose, polyvinyl pyrrolidone and polyethylene glycol. (Excipients, 2013)

1.4.5 Coatings

Tablet coatings protect tablet ingredients from deterioration by moisture in the air and make large or unpleasant-tasting tablets easier to swallow. For most coated tablets, a cellulose ether hydroxypropyl methylcellulose (HPMC) film coating is used which is free of sugar and potential allergens. Occasionally, other coating materials are used, for example synthetic polymers, shellac, corn protein zein or other polysaccharides. (Excipients, 2013)

1.4.6 Disintegrants

The purpose of a disintegrant is to facilitate the breakup of a tablet when they contact water in gastrointestinal tract.Adisintegrant is added to most tablet formulations to facilitate a breakup or disintegration of the tablet when placed in an aqueous environment. Disintegrants expand and dissolve when wet causing the tablet to break apart in the digestive tract, releasing the active ingredients for absorption.(Apu, 2010)

1.4.6.1 Determination of Flow Property of Different Groups of Excipients with Different Amounts of Disintegrants

They ensure that when the tablet is in contact with water, it rapidly breaks down into smaller fragments, facilitating dissolution. Examples of disintegrants include:

• Crosslinked polymers: cross-linked polyvinyl pyrrolidone (crospovidone), crosslinked sodium carboxymethyl cellulose (croscarmellose sodium).

• The modified starch sodium starch glycolate. (Excipients, 2013)

1.4.7 Diluents

Diluents are also known as bulking agents or fillers. Diluents added to the active ingredient in sufficient quantity to make a reasonably sized tablet. A tablet should at least 50mg and therefore very low dose drugs (diazepam, clonidine hydrochloride) will invariably require a diluent to bring the overall tablet weight to at least 50mg. This agent may not be necessary if dose of drug

per tablet is high (e.g. aspirin and certain antibiotics). Usually the range of diluents may vary from 5-80%.

Fillers or diluents typically also fill out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use.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. Plant cellulose (pure plant filler) is popular filler in tablets or hard gelatin capsules. Dibasic calcium phosphate is popular tablet filler. 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. Sometimes other noted kinds of excipients are in effect doubling in function as fillers(Apu, 2010)

1.4.7.1 Reasons for using Diluents

□□Inert substance designed to make up the required bulk of tablet when the drug dosage itself is inadequate to produce its bulk.

□□To provide better tablet properties such as:

□□Improved cohesion (maintain proper shape of tablet)

□□To permit use of direct compression manufacturing

□□To promotes flow

□□To adjust weight of tablet as per die capacity. (Apu, 2010)

1.4.7.2 Influence of diluents on bioavailability (Apu, 2010)

• Although diluents are normally thought of as inert ingredients, they can significantly affect the biopharmaceutical, chemical and physical properties of tablet. The calcium salts interfering with the absorption of tetracycline from the gastrointestinal tract. They make half the bioavailability of standard product.

• Antiepileptic drug sodium phenytoin will form poorly absorbable calcium-phenytoin complex, when calcium sulphate dihydrate used as diluent in the formulation. But using of lactose as diluent improves bioavailability of the antiepileptic drug significantly.

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

- Diluents should not react with the drug substance and moreover it should not have any effect on the functions of other excipients
- It should not have any physiological or pharmacological activity of its own
- It should have consistent physical and chemical characteristics
- It should neither promote nor contribute to segregation of the granulation or powder blend to which they are added
- It should be able to be milled (size reduced) if necessary in order to match the particle size distribution of the active pharmaceutical ingredient
- It should neither support microbiological growth in the dosage form nor contribute to any microbiological load
- It should neither adversely affect the dissolution of the product nor interfere with the bioavailability of active pharmaceutical ingredient
- It should preferably be colorless or nearly so.

Tablet diluents or fillers can be divided into three categories: (Vinensia, 2013)

i) Organic materials - Carbohydrate and modified carbohydrates:

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

· Starch and Pregelatinized Starch

· Sucrose, Manitol, Sorbitol

· Cellulose: Powdered Cellulose, Microcrystalline Cellulose

ii) Inorganic materials

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

iii) Co-processed Diluents.

1.4.7.3 Influence of diluents on incompatibility

• Sometimes diluents cause discoloration of tablet. In case of amine drugs, lactose used as dilent along with metal stearate (Magnesium stearate) used as lubricant, cause's discoloration of tablets with time. (Apu, 2010)

1.4.8. Lubricants

Lubricants are supposed to help in the reduction of friction:

□□Between particles during compression and

□□Between the walls of tablet and the walls of the cavity in which tablet was formed

The lubricants are believed to form a coat around each granule and this effect also gets extended to the tablet surface. The lubricants may show some inherent drawbacks:

□□Lessen tensile strength (may interfere with the particle – particle bonding)

□□Extension of disintegration and dissolution time (waterproofing properties)

Since primarily lubricants are required to act at the tooling or material interface, lubricants should be incorporated in the final mixing step, after granulation is complete. Concentration should not exceed to 1% for producing maximum flow rate.

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.

Common minerals like talc or silica, and fats, e.g. vegetable stearin, magnesium stearate or stearic acid are the most frequently used lubricants in tablets or hard gelatin capsules. Lubricants are agents added in small quantities to tablet and capsule formulations to improve certain processing characteristics.

There are three roles identified with lubricants as follows:

- 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.

- Anti-adherent role:

Prevent sticking to punch faces or in the case of encapsulation, lubricants

Prevent sticking to machine dosators, tamping pins, etc.

- Glidant role:

Enhance product flow by reducing interparticulate friction. (Apu, 2010)

1.4.8.1 Types (Excipients, 2013)

There are two major types of lubricants:

1. Hydrophilic

Generally poor lubricants, no glidant or anti-adherent properties.

2. Hydrophobic

Hydrophobic lubricants are generally good lubricants and are usually effective at relatively low concentrations. Hydrophobic lubricants are used much more frequently than hydrophilic compounds. E.g. magnesium stearate.

1.4.9 Glidants

Glidants are used to promote powder flow by reducing inter particle friction and cohesion. These are used in combination with lubricants as they have no ability to reduce die wall friction. The commonly used glidants are talcum, starch, colloidal silica, silicates, stearates, calcium phosphate etc. Concentration of starch is common up to 10%, but should be limited otherwise it will worsen the flow of material. Talc is a glidant which is superior to starch; its concentration should be limited because it has retardant effect on dissolution-disintegration profile. The most important and traditional glidant used is talcum (talc). Recently, silica type glidants are becoming popular due to their small particle size. Magnesium oxide and other magnesium salts are generally added as auxiliaries to silica type glidants where granules have hygroscopic inclinations. The magnesium compounds mop up the excess moisture keeping the granules dry and free flowing. (Excipients, 2013)

1.4.10 Preservatives

Some typical preservatives used in pharmaceutical formulations are

- Antioxidants like vitamin A, vitamin E, vitamin C, retinylpalmitate, and selenium
- The amino acids cysteine and methionine
- Citric acid and sodium citrate
- Synthetic preservatives like the parabens: methyl paraben and propyl paraben. (Apu, 2010)

1.4.11 Miscellaneous (Apu, 2010)

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

- Stabilisers: These are typically used, if necessary, to minimise pH dependent hydrolysis or oxidation depending on the requirement of the drug substance. To promote intimate contact of the drug with the stabiliser it is generally recommended to include the stabiliser in finely divided form at the premix stage.
- Colourants: Colouranats are added to the formulation in order to increase the patent compliance or for identification of the formulation. Usually the colurants are added in the form of insoluble powder or in the form as liquid in the granulation liquid.To obtain evenness of colouration in directly compressed formulations the use of insoluble pigments (aluminium lakes and iron oxides) is preferred. Inclusion at the premix stage can minimise “speckling” in the finished tablets. Alternatively the tablets can of course be film coated.
- Surfactants: Wetting agents such as sodium lauryl sulphate may be included, especially if the drug substance is hydrophobic.
- Flavorants: These are incorporated into the formulation to improve the flavor or give a pleasant taste to the formulation. Flavoring agents are mostly restricted to the formulations in which are intended to be released in the mouth or chewable tablets. They are usually added in along with the granules.

Table 1.3: Functions of excipients (Haywood and Glass, 2011)

Excipient	Function	Examples
Diluents	Provide bulk and enable accurate dosing of potent ingredients	Sugar compounds e.g. lactose, dextrin, glucose, sucrose, sorbitol Inorganic compounds e.g. silicates, calcium and magnesium salts, sodium or potassium chloride
Binders, compression aids, granulating agents	Bind the tablet ingredients together giving form and mechanical strength	Mainly natural or synthetic polymers e.g. starches, sugars, sugar alcohols and cellulose derivatives
Disintegrantes	Aid dispersion of the tablet in the gastrointestinal tract, releasing the active ingredient and increasing the surface area for dissolution	Compounds which swell or dissolve in water e.g. starch, cellulose derivatives and alginates, crospovidone
Glidants	Improve the flow of powders during tablet manufacturing by reducing friction and adhesion between particles. Also used as anti-caking agents.	Colloidal anhydrous silicon and other silica compounds
Lubricants	Similar action to glidants, however, they may slow disintegration and dissolution. The properties of glidants and lubricants differ, although some compounds, such as starch and talc, have both actions	Stearic acid and its salts (e.g. magnesium stearate)
Tablet coating and films	Protect tablet from the environment (air, light and moisture), increase the mechanical strength, mask taste and smell, aid swallowing, and assist in product identification. Can be used to modify release of the active ingredient. May contain flavours and colourings.	Sugar (sucrose) has now been replaced by film coating using natural or synthetic polymers. Polymers that are insoluble in acid, e.g. cellulose acetate phthalate, are used for enteric coatings to delay release of the active ingredient.
Colorants	Improve acceptability to patients, aid identification and prevent counterfeiting. Increase stability of lightsensitive drugs.	Mainly synthetic dyes and natural colours. Compounds that are themselves natural pigments of food may also be used.

1.5 Excipients used in this project (Rowe, Sheskey and Quinn, 2009)

1.5.1 Calcium phosphate

Calcium phosphate is used as diluent in the solid dosage forms. I have used this excipient in various amount keeping other types of excipients constant to see the flow property changes with variation in those formula.

1.5.1.1 Nonproprietary Names

BP: Calcium Phosphate

PhEur: Calcium Phosphate

USP-NF: Tribasic Calcium Phosphate

1.5.1.2 Empirical Formula and Molecular Weight

Ca3(PO4)2 310.20

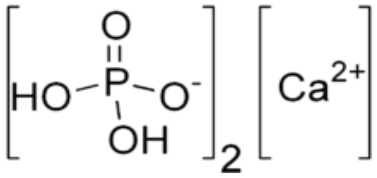
Ca5(OH)(PO4)3 502.32

1.5.1.3 Description

The PhEur 6.4 states that tribasic calcium phosphate consists of a mixture of calcium phosphates. It contains not less than 35.0% and not more than the equivalent of 40.0% of calcium. The USP32–NF27 specifies that tribasic calcium phosphate consists of variable mixtures of calcium phosphates having the approximate composition $10CaO\_3P_2O_5\_H_2O$. This corresponds to a molecular formula of $Ca_5(OH)(PO_4)_3$ or $Ca_{10}(OH)_2(PO_4)_6$.

Tribasic calcium phosphate is a white, odorless and tasteless powder.

1.5.1.4 Structural Formula



1.5.1.5 Functional Category

Anticaking agent; buffering agent; dietary supplement; glidant; tablet and capsule diluent.

1.5.1.6 Applications in Pharmaceutical Formulation or Technology

Tribasic calcium phosphate is widely used as a capsule diluent and tablet filler/binder in either direct-compression or wet-granulation processes. The primary bonding mechanism in compaction is plastic deformation. As with dibasic calcium phosphate, a lubricant and a disintegrant should usually be incorporated in capsule or tablet formulations that include tribasic calcium phosphate. In some cases tribasic calcium phosphate has been used as a disintegrant.

(1) It is most widely used in vitamin and mineral preparations

(2) As a filler and as a binder. It is a source of both calcium and phosphorus, the two main osteogenic minerals for bone health. The bioavailability of the calcium is well known to be improved by the presence of cholecalciferol. Recent research reports that combinations of tribasic calcium phosphate and vitamin D3 are a cost-effective advance in bone fracture prevention.

(3)In food applications, tribasic calcium phosphate powder is widely used as an anticaking agent.

1.5.1.7 Stability and Storage Conditions

Tribasic calcium phosphate is a chemically stable material, and is also not liable to cake during storage.

The bulk material should be stored in a well-closed container in a cool, dry place.

1.5.1.8 Incompatibilities

All calcium salts are incompatible with tetracycline antibiotics. Tribasic calcium phosphate is incompatible with tocopheryl acetate (but not tocopheryl succinate). Tribasic calcium phosphate may form sparingly soluble phosphates with hormones.

1.5.2 Talc

Talc has been used in this project as a lubricant, in different formulations its ratio has been changed slightly with the varying amount of calcium phosphate.

1.5.2.1 Nonproprietary Names

BP: Purified Talc

JP: Talc

PhEur: Talc

USP: Talc

1.5.2.2 Empirical Formula and Molecular Weight

Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4(OH)_4$. It may contain small, variable amounts of aluminum silicate and iron.

1.5.2.3 Description

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

1.5.2.4 Functional Category

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

1.5.2.5 Applications in Pharmaceutical Formulation or Technology

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent, although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbant. In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves. Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting Powder.

Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties

1.5.2.6 Stability and Storage Conditions

Talc is a stable material and may be sterilized by heating at 1608C for not less than 1 hour. It may also be sterilized by exposure toethylene oxide or gamma irradiation.

Talc should be stored in a well-closed container in a cool, dry place.

1.5.2.7 Incompatibilities

Incompatible with quaternary ammonium compounds.

1.5.3 Polyethylene glycol

1.5.3.1 Nonproprietary Names

BP: Macrogols

JP: Macrogol 400

Macrogol 1500

Macrogol 4000

Macrogol 6000

Macrogol 20000

PhEur: Macrogols

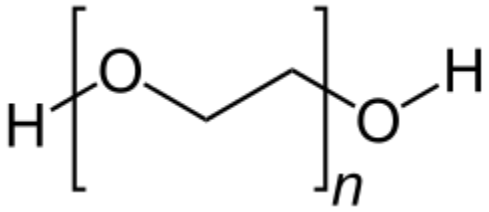
USP-NF: Polyethylene Glycol

1.5.3.2 Empirical Formula and Molecular Weight

$HOCH_2(CH_2OCH_2)mCH_2OH$ where m represents the average number of oxyethylene groups. Alternatively, the general formula $H(OCH_2CH_2)nOH$ may be used to represent polyethylene glycol, where n is a number m in the previous formula þ 1.

PEG indicates the average molecular weight of the polymer.

1.5.3.3 Structural Formula



1.5.3.4 Functional Category

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

1.5.3.5 Applications in Pharmaceutical Formulation or Technology

Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations, including parenteral, topical, ophthalmic, oral, and rectal preparations. Polyethylene glycol has been used experimentally in biodegradable polymeric matrices used in controlled-release systems.

(1) Polyethylene glycols are stable, hydrophilic substances that are essentially nonirritant to the skin. They do not readily penetrate the skin, although the polyethylene glycols are water-soluble and are easily removed from the skin by washing, making them useful as ointment bases.

(2) Solid grades are generally employed in topical ointments, with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol.

Mixtures of polyethylene glycols can be used as suppository bases,

(3) For which they have many advantages over fats. For example, the melting point of the suppository can be made higher to withstand exposure to warmer climates; release of the drug is not dependent upon melting point; the physical stability on storage is better; and suppositories are readily miscible with rectal fluids.

Polyethylene glycols have the following disadvantages: they are chemically more reactive than fats; greater care is needed in processing to avoid inelegant contraction holes in the suppositories; the rate of release of water-soluble medications decreases with the increasing molecular weight of the polyethylene glycol; and polyethylene glycols tend to be more irritating to mucous membranes than fats.

1.5.3.6 Description

The USP32–NF27 describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200–600 are liquids; grades 1000 and above are solids at ambient temperatures.

Liquid grades (PEG 200–600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste. PEG 600 can occur as a solid at ambient temperatures.

1.5.3.7 Stability and Storage Conditions

Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, and they do not become rancid.

Polyethylene glycols and aqueous polyethylene glycol solutions can be sterilized by autoclaving, filtration, or gamma irradiation.

Sterilization of solid grades by dry heat at 1508C for 1 hour may induce oxidation, darkening, and the formation of acidic degradation products. Ideally, sterilization should be carried out in an inert atmosphere. Oxidation of polyethylene glycols may also be inhibited by the inclusion of a suitable antioxidant.

If heated tanks are used to maintain normally solid polyethylene glycols in a molten state, care must be taken to avoid contamination with iron, which can lead to discoloration. The temperature must be kept to the minimum necessary to ensure fluidity; oxidation may occur if polyethylene glycols are exposed for long periods to temperatures exceeding 508C. However, storage under nitrogen reduces the possibility of oxidation.

Polyethylene glycols should be stored in well-closed containers in a cool, dry place. Stainless steel, aluminum, glass, or lined steel containers are preferred for the storage of liquid grades.

1.5.3.8 Incompatibilities

The chemical reactivity of polyethylene glycols is mainly confined to the two terminal hydroxyl groups, which can be either esterified or etherified. However, all grades can exhibit some oxidizing activity owing to the presence of peroxide impurities and secondary products formed by autoxidation.

Liquid and solid polyethylene glycol grades may be incompatible with some coloring agents.

The antibacterial activity of certain antibiotics is reduced in polyethylene glycol bases, particularly that of penicillin and bacitracin. The preservative efficacy of the parabens may also be impaired owing to binding with polyethylene glycols.

Physical effects caused by polyethylene glycol bases include oftening and liquefaction in mixtures with phenol, tannic acid, and salicylic acid. Discoloration of sulfonamides and dithranol can also occur, and sorbitol may be precipitated from mixtures. Plastics, such as polyethylene, phenol formaldehyde, polyvinyl chloride, and cellulose-ester membranes (in filters) may be softened or dissolved by polyethylene glycols. Migration of polyethylene glycol can occur from tablet film coatings, leading to interaction with core components.

1.5.4 Magnesium Stearate

1.5.4.1 Nonproprietary Names

BP: Magnesium Stearate

JP: Magnesium Stearate

PhEur: Magnesium Stearate

USP-NF: Magnesium Stearate

1.5.4.2 Empirical Formula and Molecular Weight

$C_{36}H_{70}MgO_4$ 591.24

The USP32–NF27 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate (C32H62MgO4). The PhEur describes magnesium stearate as a mixture of solid organic acids consisting mainly of variable proportions of magnesium stearate and magnesium palmitate obtained from sources of vegetable or animal origin.

1.5.4.3 Structural Formul

$[CH_3(CH_2)_{16}COO]_2Mg$

1.5.4.4 Functional Category

Tablet and capsule lubricant.

1.5.4.5 Applications in Pharmaceutical Formulation or Technology

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

1.5.4.6 Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

1.5.4.7 Stability and Storage Conditions

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

1.5.4.8 Incompatibilities

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 alkaloidalsalts.

1.5.5 CARBOXYMETHYLE CELLULOSE

1.5.5.1Nonproprietary Names

BP: Dispersible Cellulose

USP-NF: Microcrystalline Cellulose and CarboxymethylcelluloseSodium

1.5.5.2 Functional Category

Dispersing agent; emulsion stabilizer; stabilizing agent; suspending agent; thickening agent.

1.5.5.3 Applications in Pharmaceutical Formulation or Technology

Carboxymethylcellulose sodium isused to produce thixotropic gels suitable as suspending vehicles in pharmaceutical and cosmetic formulations. The sodium carboxymethylcelluloseaids dispersion and serves as a protective colloid.

Concentrations of less than 1% solids produce fluid dispersions, while concentrations of more than 1.2% solids produce thixotropicgels. When properly dispersed, it imparts emulsion stability, opacity and suspension in a variety of products, and is used in nasal sprays, topical sprays and lotions, oral suspensions, emulsions, creams andgels.Carboxymethylcellulosesodium occurs as a white or off-white odorless and tasteless hygroscopic powder containing 5–22% sodium carboxymethylcellulose. It is a water-dispersible organic hydrocolloid.

1.5.5.4 Stability and Storage Conditions

Microcrystalline cellulose and carboxymethylcellulose sodium is hygroscopic and should not be exposed to moisture. It is stable over a pH range of 3.5–11. Store in a cool, dry place. Avoid exposure to excessive heat.

1.5.5.5 Incompatibilities

Microcrystalline cellulose and carboxymethylcellulose sodium is incompatible with strong oxidizing agents.

1.5.0 APIs used in this project (Vogelpoel et al., 2004)

1.5.6 Propranolol

1.5.6.1 Indication

Propranolol hydrochloride is a well-known nonselective β-blocker, which is used in the management of angina pectoris, hypertension myocardial infarction, phaeochromocytoma, and cardiac arrhythmia's.

Solubility → Soluble (1 g dissolves in 10–30 mL) in water.

Polymorphism → Propranolol hydrochloride is known to have two polymorphic forms.

Partition Coefficient → Kasim calculated *n*-octanol/water partition coefficients using different fragmentation methods that were based on atomic contributions to lipophilicity; for uncharged propranolol, log *p* values of 2.75 and 2.65 were reported.

pK_a → A pK_a range of 9.03–9.09 was reported.

Available Dose/Tablet

Strengths currently having a MA in NL: 10, 40, and 80 mg.

1.5.6.2 Pharmacokinetic Properties

Absorption

Propranolol is almost completely absorbed after oral administration (>90%). Peak plasma concentrations are reached within 1–2 h after administration of a single dose. The absolute BA varies between 5 and 50%, due to a high pre-systemic metabolism. As a result, the BA and plasma levels show a large inter-individual variability.

The presence of an absorption window cannot be ruled out from the data reviewed here but the postulated mechanism of the permeability of propranolol: passive transport driven by the strong lipophilic nature of the substance, makes the existence of such an absorption window unlikely.

Distribution

Propranolol is rather rapidly distributed over tissues. It is highly lipophilic and moderately bound to plasma proteins (80–95%), mainly to α-1 acid glycoprotein. The distribution volume is about 4 L/kg. Studies in animals showed that propranolol is distributed into the lungs, liver, kidneys, brain, and the heart.

Metabolism and Excretion

Propranolol is almost completely metabolized in the liver. Only a small portion of the administered dose is excreted unchanged in urine and feces (1–4%). The main metabolites are naphtoxyl acetic acid (42%), 4-hydroxypropranolol (41%), and propranolol-*O*-glucuronide (17%). 4-hydroxy-propranolol is pharmacologically active and is equipotent to the parent drug. However, due to rapid conjugation, the contribution to the pharmacological effect is low. The main metabolites are metabolized by cytochrome P450. Propranolol and its metabolites are mainly excreted in urine (>90%). The elimination half-life is about 4 hr.

Table 1.4 Excipients Used in Propranolol Hydrochloride IR Tablets in NL (Abdoh et al., 2004)

Calcium carbonate
Carboxymethylcellulose sodium
Cellulose (microcrystalline)
Colloidal anhydrous silica
Croscarmellose sodium
Gelatine

Lactose anhydrate/monohydrate
Magnesium stearate
Maize starch
Potato starch
Povidone
Pregelatinized (maize) starch
Sodium carboxyamylopectin
Sodium starch glycollate
Soluble starch
Stearic acid
Talc

Dissolution

The USP 26 specification for dissolution of propranolol hydrochloride tablets is NLT 75% (Q) dissolved in 30 min in 1000 mL of dilute HCl using the basket method operated at 100 rpm.

Solubility

The pK_a value of propranolol is about 9.05. At a pH of 7.2, it is reported that propranolol is highly soluble. Therefore, solubility will not be the rate-limiting step in the absorption process of propranolol from the GI tract.

Dissolution

The differences in purpose between the dissolution tests of the Guidances and the USP were discussed under "verapamil hydrochloride." For propranolol hydrochloride solubility within the physiological pH is not critical, so the dissolution rate of the formulation will be the decisive factor for BA of this API. The USP 26 dissolution method, using dilute HCl as dissolution medium, can be expected to control insufficient dissolution from the formulation. So, the practice to carry out the batch to batch dissolution testing according to USP 26 once a formulation has been shown to be bioequivalent to the reference formulation by a BE study or by comparative dissolution studies is supported by the BCS-characteristics of this API.

1.5.7 Amlodipine

1.5.7.1 Pharmacodynamics and pharmacokinetics

Amlodipine is a low-clearance, dihydropyridine calcium antagonist. The slow rate of elimination (elimination half-life of 40-60 h) confers several pharmacokinetic characteristics that are not seen with other calcium-antagonist drugs. It has high oral bioavailability (60-80%) and accumulates to a steady-state with once-daily administration over a period of 1-1 1/2 weeks. Fluctuation of plasma drug concentration between doses is between 20 and 25% when once-daily dosing is used. Onset of effect is gradual after oral administration which is due, in part, to an intermediate rate of drug absorption (peak plasma drug concentration occurs 6-8 h after dosing) and perhaps also to the physicochemical characteristics of the drug-cell membrane-receptor interaction. The pharmacodynamic profile of the drug in hypertensive patients is consistent with the disposition of the drug. After single doses, blood pressure decreases gradually over 4-8 h and may slowly return to baseline over 24-72 h. No change in heart rate is noted after the dose as the onset is gradual and physiological reflexes are not activated. During chronic, oral, once-daily dosing blood pressure is decreased from pretreatment baseline with little fluctuation over the 24-hour dose interval. Discontinuation of amlodipine treatment results in a slow return of blood pressure to baseline over 7-10 days, with no evidence of a 'rebound' effect. Amlodipine is a low-clearance, dihydropyridine calcium antagonist which is effective for the treatment of hypertension and angina pectoris with once-daily dosing.

1.5.7.2 Mechanism of Action

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

Table 1.5 Excipients used with amlodipine (Abdoh et al., 2004)

Sodium carbonate
Calcium hydrogen phosphate
Calcium phosphate
Calcium carbonate
Calcium stearate
Zinc stearate
Magnesium stearate
Magnesium hydroxide
Magnesium carbonate

Chapter Two

LITERATURE REVIEW

2.1 Literature review

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

After three year back in 1982, a study was performed showing the effect of particle size on the compression mechanism and tensile strength of prepared tablets by two scientists, Mckenna and Mccafferty. They took some excipients for their study to check the effect of its particle size, like Sta-Rx 1500, spray-dried lactose and Avicel PH-101. In the experiment they found that declining the particle size of spray-dried lactose and Sta-Rx 1500 resulted in stronger compaction. On the other hand, particle size variation of Avicel PH-101 did not showed any impact on tablet tensile strength. Their study was concluded by identifying a statement that angle of repose and Hausner ratio measurements indicated a connection between the internal forces of friction and cohesion of the different sized powders and the tensile strength of compacts formed from them. (Mckenna and Mccafferty, 1982)

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

Then subsequent to seven years later, Tan and Newton worked on 5 pharmaceutical excipients in the middle of 1990 and found that the flowability of size fractions of 5 pharmaceutical excipients

was related to their capsule filling performance. They used angular, packing and shear tests, the samples were ranked in different relative orders of flowability. Flowability was reliant on the particle size, morphology and bulk density of the powder. They found that there was a major correlation between the values of coefficient of variation and the flow parameters of Carr's compressibility, Hausner ratio, angle of repose, Kawakita's equation constant and Jenike's flow factor. They also found that coefficient of variation was also related to the coefficient of variation of the powder bed bulk density and the variation in the compression stress.(Tan and Newton, 1990)

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

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

In 1996, Rajesh Patel andFridrunPodczeck investigated 8 microcrystalline cellulose samples on the capsule filling performance. Different sources of fine, medium and coarse grade microcrystalline cellulose were used. They determined the Kawakita constant and Hausner's ratio as the indicators of the capsule filling performance. Fine grade microcrystalline cellulose such as Avicel® PH105 cannot be used in capsule filling because of unsatisfactory flow properties. Medium and coarse grade microcrystalline cellulose can be classified as a good capsule filling excipient, but not all sources are suitable. (Patel and Podczeck, 1996)

In 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)

The same year Jivraj, Martini and Thomson observed the effect of various excipients which had been used as fillers in direct compression formulations. The tablet dosage form was considered as it accounts for more than 80% of the administered dosage form. Here the study has given emphasis on the expected result in accordance with their functionality. They want to find out the reason to give emphasis on choosing excipients depending on their function. But the study did not give enough effective finding rather stands as a narrative description. (Jivraj et al., 2000)

In the same year2000, Taylor his research fellows worked on the flow properties of typical tablet and capsule formulation excipients, active compounds as well as representative formulation blends were tested with current and novel flow measurement techniques to identify a reliable bench test to measure powder flow as a screening method in early tablet and capsule formulation development. Test methods used by them were vibrating spatula, critical orifice, and angle of repose, compressibility index, and avalanching analysis. They established empirical composite index and ranked powder flow in accordance with formulator experience. The data that they found were not reproducible from vibrating spatula and avalanching methods. (Taylor et al. 2000)

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

The same year Gabaude and his fellow researchers compared between four techniques. For the measurement of powder flow properties, two methods are considered that are packing and rearrangement under pressure methods or shear cell measurement methods. The reduction of the powder bed volume under low pressures is evaluated by two compressibility methods such as uniaxial press and volumenometer. Flow functions are determined from shear cell measurements using a JohansonIndicizer Tester. The packing coefficient obtained from reduction of the powder bed volume appears to be a reliable estimate of powder flow properties.(Gabaude et al., 2001)

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

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

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

In the year 2004, Lindberg and his research teamevaluated flow properties of four different tablet formulation having poor flowability for direct compression using five different techniques. The tableting parameters were Hausner ratio, powder rheometer and other flow behavior. The behavior of three of the formulation out of four was observed. The result was compared with the value of the flowability measurements. The correlated rank order of the formulations was considered the same with all the techniques. The measured flow properties directly reflect the behavior of the tablet formulation during powder mixture procedure.(Lindberg et al., 2004)

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

The same year 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 Variation of flow property of different set of ratio of excipients influences of the critical velocity. The influence of humidity for one of the powders was found to be negligible. In fact the process such as die opening and die filling and condition of operation such as in air or vacuum significantly change the flow behavior. (Sinka et al., 2004)

Again in the same year 2004, Jonat along with his research group studied the glidant properties of compacted hydrophilic and hydrophobic colloidal silicon dioxides and compared with respect to mixing time and mixer type using microcrystalline cellulose, pregelatinized starch and α-

lactose-monohydrate as model excipients. They also performed flowability studies, including angle of repose measurements and a novel dynamic conveyor belt method and found differences in the flow enhancement between the colloidal silicon dioxide types. They found that an influence of mixing conditions on flowability was hydrophilic colloidal silicon dioxide. They identified the influence of size and distribution of the colloidal silicon dioxide particles on the surface of the excipient, mixing time, mixer type. In addition, they found after moisture studies that colloidal silicon dioxide protects the excipients against a flowability decrease caused by humidity.(Jonat et al., 2004)

In 2005, M. C. Goheloutlined the importance of the functionality of the directly compressible adjuvants in the formulation of tablets. The co-processing is the most widely explored method for the preparation of directly compressible adjuvants because it is cost effective and can be prepared in-house based on the functionality required. Hence, the present review focuses on the properties of the co-processed directly compressible adjuvants available in the market.(Gohel, 2005)

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

Khan and Rhodes studied the effect of compressional force on the disintegration time of tablets prepared from calcium phosphate dibasic dihydrate containing various tablet disintegrants was examined. The results show that effects of compressional force on disintegration time are of two types. The first type is that of insoluble disintegrants, *e.g.*, starch and a cation-exchange resin, where the disintegration time initially shows a dramatic decrease. After this decrease, a further

increase in compressional force appears to have no effect on the disintegration time. The second type is that of soluble disintegrants, *e.g.*, calcium sodium alginate, sodium carboxy-methylcellulose, and sodium starch glycolate, where variation in compressional force has very little effect on the disintegration time. These results are discussed in terms of the differing mechanism whereby these substances act as disintegrants.(Khan and Rhodes, 2006)

Jalal and his team introduced a novel pelletizing process, spheronization, was used to prepare spherical particles for use in tablet compression. Dibasic calcium phosphate, acetaminophen, magnesium hydroxide, and sulfadiazine granulations were prepared and compressed into acceptable tablets. Tests showed that the spheronizing process resulted in an improved granulation flow rate and narrow particle-size distribution as compared to a conventionally processed wet granulation. Granulation reproducibility and change of size distribution with processing time were also studied. Tablets were compressed from all granulations, and hardness and disintegration times were determined.(Jalal, Malinowski and Smith, 2006)

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

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

have been widely used in the formulation of fast dissolving tablets. They found the non-wetting property of the hard compact central core may delay the disintegration time. They optimized the ratio of mannitol and MCC and found have optimized powder and compressibility characteristics with fast disintegrating property. They concluded that higher rate of powder flow can indirectly influence the rate of disintegration. (Jacob et al., 2007)

Gohel and his team in 2007 found out by studies, the coprocessedsuperdisintegrant proved to be superior to the physical blend in terms of flow due to size enlargement. Furthermore, the coprocessedsuperdisintegrant displayed superiority in terms of crushing strength, disintegration time, and drug dissolution. The advantages of the proposed method are easy adaptability in industry and the possibility of bypassing the existing patents in the ereas of quick disintegration and dissolution. (Gohel et al., 2007)

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

In the same year 2008, Feeley and his research fellows employed Inverse gas chromatography (IGC) to characterise the surface thermodynamic properties of two nominally equivalent batches of salbutamol sulphate. They highlighted on surface energetic changes induced on micronisation. They used powder flow avalanching analyser which explore the relationship between powder flow and the surface energetic properties. They found a result which demonstrated the potential of these techniques to detect and quantify differences in powder samples, before and after micronisation. They also indicated that the surface energy differences detected by Inverse gas chromatography (IGC) can be linked to important secondary processing properties such as powder flow. (Feeley et al., 2008)

Sawayangi, Nambu and, Nagai undergone a series of studies on pharmaceutical applications of chitin and chitosan, the fluidity and compressibility of combined powders of mannitol with chitin and chitosan, as well as the disintegration properties of tablets made from these powders were investigated in comparison with those of crystalline cellulose with mannitol. The fluidity of the

combined powders with chitin and chitosan was a little greater than that of the powder with crystalline cellulose. At more than 30% addition of chitin, chitosan or crystalline cellulose, tablets were easily formed. Tablets containing less than 60% chitin or chitosan passed the disintegration test of JP X. It is suggested that chitin and chitosan, as well as crystalline cellulose, may be suitable as diluents for chewable, sublingual or oral mucosal tablets prepared by direct compression processes.(Sawayangi, Nambu and, Nagai, 2008)

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

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

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

M. Autamashih and his team in 2011, studied the effect of anhydrous calcium phosphate, an efflorescent pharmaceutical powder of reduced moisture content, ideal for moisture-sensitive

materials; and the comparative binding effects of maize starch, polyvinylpyrrolidone and gelatin were investigated in the tablet formulation of the deliquescent crude extract of the leaves of Vernoniagalamensis (Asteraceae). The mechanical strengths and drug release properties of the designed tablets were assessed using the crushing strength friability, disintegration time ratio (CSFR: DT) and dissolution rate. An increase in binder concentration led to an increase in crushing strength, decrease in friability and increase in disintegration time of the tablets. Anhydrous calcium phosphate used as diluent along with polyvinylpyrrolidone as binder produced the best quality tablets in terms of the CSFR: DT ratioand dissolution rate as compared to the diluent used with maize starch and gelatin as binders.(Autamashih et al., 2011)

The objective of a medicinal formulation development project is to deliver drug to the patient in the required amount, at the required rate, consistently within a batch, from batch to batch, and over the product's shelf life evaluated by Hardik Patel, Viral Shah and UmeshUpadhyay in 2011. To produce a drug substance in a final dosage form requires pharmaceutical ingredients. In selecting excipients for pharmaceutical; dosage forms and drug products the development pharmacist should be certain that standards exist and are available to assure the consistent quality and functioning of the excipient from lot to lot. The development of new materials for use as pharmaceutical excipients requires the demonstration of the absence of toxicity and freedom from adverse reactions. The selection and testing of nonactive ingredients or excipient in the design of drug dosage form present to the formulator the challenge of predictive foresight. While the ability to solve problems when they occur is a valuable attribute, the ability to prevent the problem through adequate experimental design is a virtue. Newer excipients provide the means for simplifying formulation development, and improving overall operational costs while preserving the quality that is expected by the industry.(Patel, Shah andUpadhyay, 2011)

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

In the same year 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)

Most recently Vanarase, Osorio, and Muzzio focused on two aspects of continuous powder mixing such as characterizing the effects of material properties on the bulk powder flow behavior, and developing continuous blending strategies suitable for cohesive materials. The relative effects of process parameters and material properties on the bulk powder flow behavior were analyzed by a PLS analysis of the output parameters. It includes mean residence time, and axial dispersion coefficient. The function of input parameters is impeller speed, flow rate, bulk density and cohesion. The study showed that means residence time was mainly affected by the bulk density and impeller speed. On the other hand, the axial dispersion coefficient was affected by impeller speed and cohesion. The research also demonstrated that a combination of high shear and low shear mixing with high-shear mixing as a first step exhibited an optimal mixing strategy for blending cohesive materials. (Vanarase et al., 2013)

In that year 2013, Crouter and Briens investigated the flowability of MCC, HPMC, CMC, PVP, corn starch, and potato starch. Flowability of MCC, CMC and PVP decreased after a critical moisture content and for corn starch, it was increased. Flowability of HPMC was not changed that much. The moisture decreased flowability by forming stronger interparticle liquid bridges and increased flowability by acting as a lubricant. The dynamic density of the celluloses and PVP decreased linearly with increasing moisture content as the particles swelled with water. The starches also swelled and decreased in dynamic density, but only after a moisture content corresponding to monolayer coverage of water around the particles had been reached. (Crouter and Briens, 2013)

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

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

Chapter Three

MATERIALS AND METHODS

3.1 API and excipient collection

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

3.2 List of excipient used

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

Table 3.1: List of excipients with their individual source

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

3.3 Equipment and instruments

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

Fig 3.1: Analytical balance

3.4 Apparatus

All the apparatus used in this research are listed below:

Table 3.2: Name of apparatus used

Serial no	Name of apparatus
1.	Beaker (100 ml)
2.	Test tubes with stands
3.	Measuring cylinder (50ml)
4.	Funnel
5.	Mortar pestle
6.	Spatula
7.	Stand
8.	Glass rod
9.	Aluminum foil paper
10.	Cling Wrap
11.	Scale
12.	White paper
13.	Masking tape

3.5 Methods

3.5.1 Preparation of Formulation sets of excipients:

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

I weighed all the ingredients in analytical balance then mixed them uniformly by mortar and pestle and placed into a properly cleaned dry test tube. At first, I added all 4 types of excipients in a definite percentage to make that a 10g excipients mixture. After that I made a 3g formulation of excipients from that 10g formula and adding calcium phosphate as diluent in a definite percentage. A total of four sets of sample mixture of 3g were set up for further procedure that is the determination of flow property.

Again four sets of excipient mixtures were prepared and in those formulas I added API amlodipine to determine the changes in flow properties.

Another four sets of formulas were prepared and added propranolol as API to determine the changes in flow properties.

Measured individual flow properties by observing its bulk volume, tapped volume, which ultimately yielded carr's index, hausner ratio. Angle of repose was determined as well by measuring the height and diameter of powder pile. The process was continued to evaluate the difference in flow properties while adding different ratio of calcium phosphate. In this research I also used 0.0625g of two API (Amlodopine and Propanolol) to see the difference in flow characteristics of APIs and excipients.

3.5.2 Preparation on formula 1 (F1)

Table 3.3: Amounts of excipients in formula one with justification

Formula	Excipients	Justification	Amount in the formula
Formula 1	Poly ethylene glycol Carboxy methyl cellulose Mg stearate Talc	Binder Disintegrant Antiadherent Lubricant	25% 15% 10% 10%

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

Ingredients	Amount in 10 g
Poly ethylene glycol	3.5 g
Carboxy methyl cellulose	2.5 g
Mg stearate	1 g
Talc	1 g
	Total 10 g

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

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

Ratio	Calcium phosphate: F1 %	Amount of calcium phosphate:F1(in g)
1	40 : 60	1.2 : 1.8
2	45 : 55	1.35 : 1.65
3	50 : 50	1.5 : 1.5
4	55 : 45	1.65 : 1.35
5	60 : 40	1.8 : 1.2

3.5.3 Preparation of formula 2 (F2)

Table 3.6: Amounts of excipients in formula two with justification

Formula	Excipients	Justification	Amount in the formula
Formula 2	Poly ethylene glycol Carboxy methyl cellulose Mg stearate Talc	Binder Disintegrant Antiadherent Lubricant	20% 15% 10% 10%

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

Ingredients	Amount in 10 g
Poly ethylene glycol	3.5 g
Carboxy methyl cellulose	2.5 g
Mg stearate	1.5 g
Talc	1.5 g
	Total: 10 g

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

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

Ratio	Calcium phosphate: F2 %	Amount of calcium phosphate:F2(in g)
1	45 : 55	1.35 : 1.65
2	50 : 50	1.5 : 1.5
3	55 : 45	1.65 : 1.35
4	60 : 40	1.8 : 1.2
5	65 : 35	1.95 : 1.05

3.5.4 Preparation of formula 3

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

Table 3.9: Amounts of excipients in formula three with justification

Formula	Excipients	Justification	Amount in the formula
Formula 3	Poly ethylene glycol Carboxy methyl cellulose Mg stearate Talc	Binder Disintegrant Antiadherent Lubricant	20% 15% 10% 10%

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

Ingredients	Amount in 10 g
Poly ethylene glycol	3.5 g
Carboxy methyl cellulose	2.5 g
Mg stearate	1.5 g
Talc	1.5 g
	Total: 10 g

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

Ratio	Calcium phosphate: F3	Amount of calcium phosphate:F3(in g)
1	38 : 62	1.14 : 1.86
2	44 : 56	1.32 : 1.68
3	50 : 50	1.5 : 1.5
4	56 : 44	1.68 : 1.32
5	62 : 38	1.86 : 1.14

3.5.5 Preparation of formula 4

Table 3.12: Amounts of excipients in formula four with justification

Formula	Excipients	Justification	Amount in the formula
Formula 3	Poly ethylene glycol	Binder	20%
	Carboxy methyl cellulose	Disintegrant	15%
	Mg stearate	Antiadherent	10%
	Talc	Lubricant	10%

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

Ingredients	Amount in 10 g
Poly ethylene glycol	3.5 g
Carboxy methyl cellulose	2.5 g
Mg stearate	1.5 g
Talc	1.5 g
	Total: 10 g

Table: 3.14: Amount of calcium phosphate and F4 in differentratio in 3g

Ratio	Calcium phosphate: F4 %	Amount of calcium phosphate:F4(in g)
1	36 : 64	1.08 : 1.92
2	42 : 58	1.26 : 1.74
3	48 : 52	1.44 : 1.56
4	54 : 46	1.62 : 1.38
5	60 : 40	1.8 : 1.2

3.6 Flow property measurement

3.6.1 Determination of bulk volume:

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

3.6.2 Determination of tapped volume:

- After taking the bulk volume, tapped volume was taken. At first, the measuring cylinder containing the mixtures of ingredient was tapped manually 50 times on a flat surface.]
- The tapping was achieved by raising the cylinder to a constant distance and then allowed to drop.
- The difference in the volume was observed and documented.

- The same process was done five times and took the average of them to find out the most acceptable data.

3.6.3 Determination of tapped volume:

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

Compressibility index:

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

Hausner ratio:

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

3.6.4 Measurement of Angle of repose:

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

- A funnel made up of plastic, glass or stainless steel was set with the holding stand tightly at first.
- The funnel was fixed in a place, 4 cm above the bench surface.
- Then a piece of clean white paper was placed on the bench surface.
- The mixture of the running test tube was poured through the funnel without incorporating external pressure or stress.
- The powder mixture formed a cone on the white paper.
- After the cone from 3g of sample was built, height of the granules forming the cone (h) measured in cm and the radius (r) of the base in cm was measured by a scale.
- The angle of repose was calculated by the given formula and documented.
- The same process was run for five times and took the average of them to get the most acceptable data.

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

Chapter Four

Results

4.1. Calculation of individual excipients flow properties:

The flow property of four formulations individual excipients were measured by calculating their Carr's index, Hausner ratio and angle of repose.

Formula 1(excipients with fixed diluent): For calculating Carr's index and Hausner ratio, their individual bulk volume and tapped volume were measured five times and the average value was taken. The observed value is given below:

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

Ratio	Bulk volume V_o(ml)	Most acceptable volume of V_o (ml)	Tapped volume V_r(ml)	Most acceptable volume of V_r(ml)	Hausner ratio	Carr's index
Ratio 1	14.5	14.5	10.7	10.7	1.45	30.97
	14.2		10.8			
	14.2		10.9			
	14.1		10.7			
	14.3		10.9			
Ratio 2	14.0	14	9.7	9.7	1.44	30.71
	14.0		9.8			
	13.9		9.8			
	13.8		9.9			
	13.9		10			
Ratio 3	14.0	14	9.8	9.8	1.43	30
	14.0		9.8			
	13.9		9.9			
	13.8		9.9			
	13.9		10			
Ratio 4	12.6	12.6	9.3	9	1.4	28.56
	12.5		9.2			
	12.4		9.1			
	12.3		9.0			
	12.3		9.0			
Ratio 5	12.1	12.1	9.0	8.7	1.39	28.1
	12.1		8.7			
	12.0		8.7			
	12.0		8.8			
	11.9		8.7			

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

Table 4.2: Calculation of Angle of repose for formula 1

Ratio	Height (h) cm	Avg.Height(h)cm	Radius(r)cm	Average Radius(r) cm	Angle of Repose
Ratio 1	2.2	2.24	2.1875	2.23	45.13
	2.1		2.25		
	2.3		2.3		
	2.3		2.2625		
	2.2		2.15		
Ratio 2	2.5	2.5	2.54	2.526	44.7
	2.7		2.5		
	2.6		2.6		
	2.3		2.325		
	2.5		2.425		
Ratio 3	2.2	2.12	2.4375	2.2531	43.26
	2		2.2625		
	2.3		2.28		
	2.1		2.1125		
	1.8		2.173		
Ratio 4	2.2	2.12	2.275	2.3325	42.27
	2		2.3		
	2.3		2.7		
	2.1		2.225		
	1.8		2.1625		
Ratio 5	2.1	1.94	2.4625	2.1875	41.56
	2		2.2325		
	1.9		2.075		
	1.8		2.025		
	1.9		2.1375		

Formula 2(excipients with fixed diluent): For calculating Carr's index and Hausner ratio, their individual bulk volume and tapped volume were measured five times and the average value was taken. The observed value is given below:

Table 4.3: Values of individual excipients for determining Carr's index and Hausner ratio for formula 2

Ratio	Bulk volume V_o(ml)	Most acceptable volume of V_o (ml)	Tapped volume V_r (ml)	Most acceptable volume of V_r (ml)	Hausner ratio	Carr's index
Ratio 1	8.5	8.5	6.1	6.1	1.39	28.24
	8.3		6.3			
	8.4		6.2			
	8.5		6.3			
	8.3		6.1			
Ratio 2	8.2	8.3	6.2	6	1.38	27.71
	8.3		6.2			
	8.3		6			
	8.1		6.3			
	8.0		6.3			
Ratio 3	8	8.2	6	6	1.37	26.82
	8.2		6			
	8.1		6.2			
	7.8		6			
	7.9		6.3			
Ratio 4	8	8.1	6	6.0	1.35	25.93
	8		6			
	8.1		6			
	7.8		6.1			
	7.9		6.2			
Ratio 5	8	8	6.3	6	1.33	25
	8		6.2			
	8		6.1			
	7.8		6.1			
	7.9		6			

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 formula 2

Ratio	Height (h) cm	Avg. Height (h) cm	Radius (r) cm	Average Radius (r)cm	Angle of Repose
Ratio 1	2	2	2.225	2.19	42.40
	2.1		2.225		
	2		2.2		
	1.9		2.15		
	2		2.15		
Ratio 2	1.8	1.9	2.1375	2.22	40.56
	2		2.175		
	1.9		2.1875		
	2		2.3		
	1.8		2.3		
Ratio 3	1.7	1.78	2.075	2.0825	40.52
	1.8		2.0875		
	1.8		2		
	1.8		2.1125		
	1.8		2.1375		
Ratio 4	1.7	1.76	2.1125	2.1025	39.93
	1.7		2.1625		
	1.8		2.0125		
	1.8		2.075		
	1.8		2.15		
Ratio 5	1.7	1.7	2.2375	2.195	37.76
	1.6		2.225		
	1.6		2.075		
	1.8		2.15		
	1.8		2.1375		

Formula 3(excipients with fixed diluent): For calculating Carr's index and Hausner ratio, their individual bulk volume and tapped volume were measured five times and the average value was taken. The observed value is given below:

Table 4.5: Values of individual excipients for determining Carr's index and Hausner ratio for formula 3

Ratio	Bulk volume V_o(ml)	Most acceptable volume of V_o (ml	Tapped volume V_r (ml)	Most acceptable volume of V_r (ml)	Hausner ratio	Carr's index
Ratio 1	6.5	6.5	5.7	5.2	1.25	20
	6.4		5.4			
	6.2		5.5			
	6.3		5.2			
	6.3		5.3			
Ratio 2	6.7	6.7	5.7	5.4	1.24	19.4
	6.7		5.4			
	6.5		5.5			
	6.6		5.4			
	6.7		5.5			
Ratio 3	6.4	6.4	5.7	5.3	1.20	17.19
	6.3		5.4			
	6.3		5.5			
	6.4		5.4			
	6.2		5.3			
Ratio 4	6.5	6.5	5.9	5.5	1.18	15.38
	6.5		6.3			
	6.4		5.9			
	6.3		6.2			
	6.5		5.5			
Ratio 5	6.8	6.8	5.9	5.9	1.15	13.24
	6.7		5.9			
	6.6		6.2			
	6.7		6.1			
	6.8		6.1			

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:

Table 4.6: Calculation of Angle of repose for formula 3

Ratio	Height(h)cm	Avg.Height(h)cm	Radius(r) cm	AverageRadius(r)cm	Angle of Repose
Ratio 1	1.5	1.46	2.225	2.14	34.3
	1.4		2.2		
	1.4		2.0375		
	1.4		2.05		
	1.6		2.1875		
Ratio 2	1.4	1.36	2.0375	2.1375	32.47
	1.4		2.1875		
	1.4		2.1125		
	1.3		2.125		
	1.3		2.225		
Ratio 3	1.3	1.24	2.1	2.0925	30.65
	1.3		2.125		
	1.2		2		
	1.2		2.1125		
	1.2		2.125		
Ratio 4	1.2	1.2	2	2.085	29.92
	1.2		2.0375		
	1.2		2.0375		
	1.3		2.175		
	1.1		2.175		
Ratio 5	1.1	1.1	2.075	2.02	28.57
	1.1		2.025		
	1.1		2.075		
	1.1		2		
	1.1		2.05		

Formula 4(excipients with fixed diluent): For calculating Carr's index and Hausner ratio, their individual bulk volume and tapped volume were measured five times and the average value was taken. The observed value is given below:

Table 4.7: Values of individual excipients for determining Carr's index and Hausner ratio for formula 4

Ratio	Bulk volume V_o(ml)	Most acceptable volume of V_o (ml	Tapped volume V_r (ml)	Most acceptable volume of V_r (ml)	Hausner ratio	Carr's index
Ratio 1	8.5	8.5	6.7	6.4	1.32	24.71
	8.3		6.4			
	8.4		6.6			
	8.5		6.5			
	8.3		6.5			
Ratio 2	8.4	8.5	6.7	6.5	1.31	23.53
	8.3		6.8			
	8.3		6.6			
	8.1		6.5			
	8.5		6.5			
Ratio 3	8	8.2	6.7	6.5	1.26	20.73
	8.2		6.8			
	8.1		6.6			
	7.8		6.5			
	7.9		6.5			
Ratio 4	7.8	7.9	6.5	6.3	1.25	20.25
	7.7		6.4			
	7.6		6.3			
	7.8		6.5			
	7.9		6.3			
Ratio 5	8	8	6.5	6.5	1.23	18.75
	8		6.6			
	8		6.7			
	7.8		7.0			
	7.9		7.0			

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

Table 4.8: Calculation of Angle of repose for formula 4

Ratio	Height (h) cm	Avg. Height (h) cm	Radius (r) cm	Average Radius (r)cm	Angle of Repose
Ratio 1	1.5	1.52	2.1125	2.2025	34.61
	1.5		2.1875		
	1.5		2.41255		
	1.4		2.1625		
	1.7		2.1375		
Ratio 2	1.7	1.4	2.075	2.0325	34.56
	1.4		1.9625		
	1.3		2.1125		
	1.3		2.05		
	1.3		1.9625		
Ratio 3	1.3	1.26	2.1	2.0925	30.65
	1.3		2.125		
	1.2		2		
	1.2		2.1125		
	1.2		2.125		
Ratio 4	1.2	1.14	1.9375	1.9625	30.15
	1.2		1.9325		
	1.1		1.8875		
	1.1		2.025		
	1.1		2.025		
	1.2		2.0375		

Ratio 5	1.2	1.14	2.1625	2.0575	28.99
	1.1		1.9875		
	1.1		2.125		
	1.1		1.975		

Amlodipine Formula 1: For calculating Carr's index and Hausner ratio, their individual bulk volume and tapped volume were measured five times and the average value was taken. The observed value is given below:

Table 4.9: Values of individual excipients for determining Carr's index and Hausner ratio for Amlodipine formula 1

Ratio	Bulkvolume V_o(ml)	Most acceptable volumeofV_o(ml)	Tapped volumeV_r(ml)	Most acceptable volume of V_r(ml)	Hausner ratio	Carr's index
Ratio 1	3.9	4	2.7	2.7	1.48	32.5
	3.8		2.9			
	4		2.9			
	4		2.8			
	4		2.7			
Ratio 2	3.5	3.5	2.4	2.4	1.46	31.43
	3.4		2.7			
	3.2		2.5			
	3.3		2.6			
	3.5		2.4			
Ratio 3	3.3	3.3	2.5	2.3	1.44	30.30
	3.1		2.4			
	3.1		2.3			
	3.2		2.4			
	3.3		2.5			
Ratio 4	3.4	3.4	2.4	2.4	1.42	29.41
	3.1		2.7			
	3.1		2.6			
	3.2		2.5			
	3.3		2.4			
Ratio 5	3.3	3.3	2.4	2.4	1.38	27.27
	3.1		2.7			
	3.1		2.6			
	3.2		2.5			
	3.3		2.4			

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:

Table 4.10: Calculation of Angle of repose for Amlodipine formula 1

Ratio	Height (h) cm	Avg. Height (h) cm	Radius (r) cm	Average Radius (r)cm	Angle of Repose
Ratio 1	1.5	1.44	1.45	1.452	44.76
	1.5		1.43		
	1.4		1.45		
	1.4		1.53		
	1.4		1.4		
Ratio 2	1.4	1.396	1.41	1.416	44.59
	1.4		1.41		
	1.4		1.45		
	1.4		1.43		
	1.3		1.38		
Ratio 3	1.3	1.32	1.41	1.414	43.03
	1.3		1.45		
	1.3		1.44		
	1.3		1.38		
	1.4		1.39		
Ratio 4	1.2	1.32	1.48	1.474	41.85
	1.3		1.48		
	1.3		1.46		
	1.3		1.5		
	1.3		1.45		
Ratio 5	1.4	1.34	1.48	1.51	41.63
	1.4		1.46		
	1.3		1.45		
	1.3		1.62		
	1.3		1.5		

Amlodipine Formula 2: For calculating Carr's index and Hausner ratio, their individual bulk volume and tapped volume were measured five times and the average value was taken. The observed value is given below:

Table 4.11: Values of individual excipients for determining Carr's index and Hausner ratio for Amlodipine formula 2

Ratio	Bulk volume V_o(ml)	Most acceptable volume of V_o (ml	Tapped volume V_r (ml)	Most acceptable volume of V_r (ml)	Hausner ratio	Carr's index
Ratio 1	4.2	4.2	3	3	1.40	28.57
	4.1		3.1			
	4.2		3.2			
	4		3.3			
	4.1		3			
Ratio 2	4	4	3.1	2.9	1.38	27.5
	4		3.2			
	3.7		3			
	3.6		2.9			
	3.9		2.9			
Ratio 3	3.7	3.7	2.8	2.7	1.37	27.03
	3.4		2.7			
	3.7		2.9			
	3.6		2.7			
	3.5		2.9			
Ratio 4	3.7	3.8	3	2.8	1.36	26.32
	3.6		2.9			
	3.8		2.8			
	3.7		2.8			
	3.6		2.9			
Ratio 5	3.7	3.9	3	2.9	1.35	25.64
	3.6		2.9			
	3.8		3			
	3.7		3			
	3.9		2.9			

The 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:

Table 4.12: Calculation of Angle of repose for Amlodipine formula 2

Ratio	Height (h) cm	Avg. Height (h) cm	Radius (r) cm	Average Radius (r)cm	Angle of Repose
Ratio 1	1.5	1.4	1.45	1.5	43.03
	1.3		1.54		
	1.4		1.44		
	1.4		1.51		
	1.4		1.55		
Ratio 2	1.4	1.34	1.48	1.51	41.63
	1.4		1.46		
	1.3		1.45		
	1.3		1.62		
	1.3		1.5		
Ratio 3	1.3	1.26	1.41	1.434	41.31
	1.3		1.5		
	1.3		1.43		
	1.2		1.38		
	1.2		1.45		
Ratio 4	1.2	1.2	1.45	1.5	39.65
	1.1		1.41		
	1.2		1.4		
	1.1		1.53		
	1.3		1.45		
Ratio 5	1.2	1.16	1.44	1.5	37.72
	1.2		1.55		
	1.2		1.51		
	1.1		1.55		
	1.1		1.45		

Amlodipine Formula 3: For calculating Carr's index and Hausner ratio, their individual bulk volume and tapped volume were measured five times and the average value was taken. The observed value is given below:

Table 4.13: Values of individual excipients for determining Carr's index and Hausner ratio for Amlodipine formula 3

Ratio	Bulk volume V_o(ml)	Most acceptable volume of V_o (ml	Tapped volume V_r (ml)	Most acceptable volume of V_r(ml)	Hausner ratio	Carr's index
Ratio 1	3.7	4	3.7	3.2	1.25	20
	4		3.4			
	3.7		3.5			
	3.9		3.2			
	3.8		3.3			
Ratio 2	3.7	4.1	3.3	3.3	1.24	19.51
	4		3.4			
	4.1		3.5			
	3.9		3.4			
	3.8		3.5			
Ratio 3	3.7	4	3.3	3.3	1.21	17.5
	4		3.4			
	3.7		3.5			
	3.9		3.4			
	3.8		3.5			
Ratio 4	4	4.1	3.5	3.3	1.20	17.07
	4		3.4			
	4.1		3.5			
	3.9		3.4			
	3.8		3.5			
Ratio 5	4.1	4.2	3.9	3.6	1.16	14.29
	4		3.9			
	4.2		3.7			
	3.9		3.6			
	3.8		3.8			

The angle of repose of Amlodipine 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:

Table 4.14: Calculation of Angle of repose for Amlodipine formula 3

Ratio	Height (h) cm	Avg. Height(h) cm	Radius (r) cm	Average Radius (r)cm	Angle of Repose
Ratio 1	1.1	1.04	1.45	1.5	34.74
	1		1.55		
	1.1		1.55		
	1		1.5125		
	1		1.4375		
Ratio 2	1.1	1	1.4125	1.4475	34.64
	.9		1.525		
	.9		1.45		
	.9		1.4		
	.9		1.45		
Ratio 3	1	1.02	1.5625	1.5675	33.05
	1		1.5625		
	1		1.5875		
	1		1.575		
	1.1		1.55		
Ratio 4	.9	.84	1.45	1.4125	30.74
	.9		1.4125		
	.8		1.375		
	.8		1.3875		
	.8		1.4375		
Ratio 5	.9	.84	1.4625	1.4625	29.87
	.9		1.475		
	.8		1.425		
	.8		1.475		
	.8		1.4875		

Amlodipine Formula 4: For calculating Carr's index and Hausner ratio, their individual bulk volume and tapped volume were measured five times and the average value was taken. The observed value is given below:

Table 4.15: Values of individual excipients for determining Carr's index and Hausner ratio for Amlodipine formula 4

Ratio	Bulk volume V_o(ml)	Most acceptable volume of V_o (ml	Tapped volume V_r (ml)	Most acceptable volume of V_r (ml)	Hausner ratio	Carr's index
Ratio 1	3.2	3.4	2.9	2.6	1.32	23.52
	3.1		2.8			
	3.2		2.7			
	3.2		2.9			
	3.4		2.6			
Ratio 2	3.7	4	3.1	3.1	1.30	22.5
	4		3.1			
	4		3.3			
	3.9		3.3			
	3.8		3.2			
Ratio 3	3.2	3.4	3	2.7	1.26	20.59
	3.1		2.9			
	3.2		2.8			
	3.2		2.7			
	3.4		2.9			
Ratio 4	3.5	3.5	3	2.8	1.25	20
	3.2		2.9			
	3.2		2.8			
	3.4		2.8			
	3.5		2.9			
Ratio 5	3.2	3.6	3.1	2.9	1.24	19.44
	3.6		2.9			
	3.4		3			
	3.4		3.3			
	3.5		3.2			

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

Table 4.16: Calculation of Angle of repose for Amlodipine formula 4

Ratio	Height (h) cm	Avg. Height (h) cm	Radius (r) cm	Average Radius (r)cm	Angle of Repose
Ratio 1	1	1.05	1.45	1.475	35.48
	1.1		1.3		
	1.1		1.46		
	1		1.475		
	1.3		1.48		
Ratio 2	1	1.05	1.62	1.5165	34.07
	1		1.45		
	1		1.475		
	1.1		1.5375		
	1.1		1.5		
Ratio 3	1	.88	1.3625	1.39	32.34
	.9		1.35		
	.9		1.3625		
	.8		1.4125		
	.8		1.4625		
Ratio 4	.9	.84	1.5125	1.5025	29.79
	.9		1.5		
	.9		1.5		
	.8		1.525		
	.8		1.475		
Ratio 5	.9	.82	1.5875	1.545	27.96
	.8		1.5		
	.8		1.5625		
	.8		1.5375		
	.8		1.5375		

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

Table 4.17: Values of individual excipients for determining Carr's index and Hausner ratio for Propranolol formula 1

Ratio	Bulk volume V_o(ml)	Most acceptable volume of V_o (ml)	Tapped volume V_r (ml)	Most acceptable volumeofV_r(ml)	Hausner ratio	Carr's index
Ratio 1	3.9	4	2.7	2.7	1.48	32.5
	3.8		2.9			
	4		2.9			
	4		2.8			
	4		2.7			
Ratio 2	3.5	3.5	2.4	2.4	1.46	31.43
	3.4		2.7			
	3.2		2.5			
	3.3		2.6			
	3.5		2.4			
Ratio 3	3.2	3.2	2.5	2.2	1.45	31.25
	3.1		2.4			
	3.1		2.3			
	3.2		2.2			
	3.2		2.5			
Ratio 4	3.3	3.3	2.6	2.3	1.44	30.30
	3.1		2.7			
	3.1		2.3			
	3.2		2.5			
	3.3		2.5			
Ratio 5	3.4	3.4	2.4	2.4	1.42	29.41
	3.1		2.7			
	3.1		2.6			
	3.2		2.5			
	3.3		2.4			

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

Table 4.18: Calculation of Angle of repose for Propranolol formula 1

Ratio	Height (h) cm	Avg. Height (h) cm	Radius (r) cm	Average Radius (r)cm	Angle of Repose
Ratio 1	1.5	1.46	1.45	1.452	45.16
	1.4		1.53		
	1.5		1.45		
	1.4		1.4		
	1.5		1.5		
Ratio 2	1.5	1.42	1.38	1.416	45.08
	1.4		1.45		
	1.5		1.41		
	1.4		1.41		
	1.3		1.43		
Ratio 3	1.3	1.34	1.38	1.414	43.46
	1.4		1.45		
	1.3		1.41		
	1.4		1.44		
	1.3		1.39		
Ratio 4	1.4	1.32	1.48	1.51	41.76
	1.3		1.46		
	1.3		1.45		
	1.3		1.62		
	1.3		1.5		
Ratio 5	1.3	1.24	1.45	1.474	40.07
	1.2		1.5		
	1.3		1.48		
	1.2		1.46		
	1.2		1.48		

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

Table 4.19: Values of individual excipients for determining Carr's index and Hausner ratio for Propranolol formula 2

Ratio	Bulk volume V_o(ml)	Most acceptable volume of V_o (ml	Tapped volume V_r (ml)	Most acceptable volume of V_r (ml)	Hausner ratio	Carr's index
Ratio 1	4.2	4.3	3.1	3.1	1.39	27.91
	4.3		3.1			
	4.2		3.2			
	4		3.3			
	4.1		3.2			
Ratio 2	4	4	3.1	2.9	1.38	27.5
	4		3.2			
	3.7		3			
	3.6		2.9			
	3.9		2.9			
Ratio 3	3.3	3.3	2.4	2.4	1.38	27.27
	3.1		2.7			
	3.1		2.6			
	3.2		2.5			
	3.3		2.4			
Ratio 4	3.7	3.7	2.8	2.7	1.37	27.03
	3.4		2.7			
	3.7		2.9			
	3.6		2.7			
	3.5		2.9			
Ratio 5	3.7	3.9	3	2.9	1.35	25.64
	3.6		2.9			
	3.8		3			
	3.7		3			
	3.9		2.9			

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

Table 4.20: 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
Ratio 1	1.5	1.42	1.45	1.5	43.43
	1.4		1.54		
	1.4		1.44		
	1.4		1.51		
	1.4		1.55		
Ratio 2	1.4	1.32	1.48	1.51	41.76
	1.3		1.46		
	1.3		1.45		
	1.3		1.62		
	1.3		1.5		
Ratio 3	1.4	1.28	1.41	1.434	41.75
	1.3		1.5		
	1.3		1.43		
	1.2		1.38		
	1.2		1.45		
Ratio 4	1.2	1.24	1.45	1.5	39.58
	1.1		1.41		
	1.2		1.4		
	1.4		1.53		
	1.3		1.45		
Ratio 5	1.2	1.18	1.44	1.5	38.19
	1.2		1.55		
	1.2		1.51		
	1.1		1.55		
	1.2		1.45		

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

Table 4.21: Values of individual excipients for determining Carr's index and Hausner ratio for Propranolol formula 3

Ratio	Bulk volume V_o(ml)	Most acceptable volume of V_o (ml	Tapped volume V_r (ml)	Most acceptable volume of V_r (ml)	Hausner ratio	Carr's index
Ratio 1	3.7	3.9	3.7	3.1	1.26	20.51
	3.9		3.4			
	3.7		3.5			
	3.9		3.2			
	3.8		3.1			
Ratio 2	3.7	4	3.3	3.2	1.25	20
	4		3.4			
	4		3.2			
	3.9		3.4			
	3.8		3.5			
Ratio 3	4	4.1	3.3	3.3	1.24	19.51
	4.1		3.4			
	3.7		3.5			
	3.9		3.4			
	3.8		3.5			
Ratio 4	3.7	3.8	3.5	3.1	1.23	18.42
	3.8		3.1			
	3.7		3.3			
	3.7		3.4			
	3.8		3.1			
Ratio 5	3.7	3.9	3.2	3.2	1.22	17.94
	3.8		3.3			
	3.7		3.4			
	3.9		3.2			
	3.8		3.3			

The angle of repose of Propranolol 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:

Table 4.22: Calculation of Angle of repose for Propranolol formula 3

Ratio	Height (h) cm	Avg. Height (h) cm	Radius (r) cm	Average Radius (r)cm	Angle of Repose
Ratio 1	1.1	1.06	1.45	1.5	35.25
	1		1.55		
	1.1		1.55		
	1.1		1.5125		
	1		1.4375		
Ratio 2	1	1.04	1.5625	1.5675	33.56
	1		1.5625		
	1		1.5875		
	1.1		1.575		
	1.1		1.55		
Ratio 3	1.1	.96	1.4125	1.4475	33.55
	1		1.525		
	.9		1.45		
	.9		1.4		
	.9		1.45		
Ratio 4	.9	.88	1.45	1.4125	31.92
	.9		1.4125		
	.8		1.375		
	1		1.3875		
	.8		1.4375		
Ratio 5	.9	.84	1.4625	1.4625	29.87
	.9		1.475		
	.8		1.425		
	.8		1.475		
	.8		1.4875		

Propranolol formula 4: For calculating Carr's index and Hausner ratio, their individual bulk volume and tapped volume were measured five times and the average value was taken. The observed value is given below:

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

Ratio	Bulk volume V_o(ml)	Most acceptable volume of V_o (ml	Tapped volume V_r (ml)	Most acceptable volume of V_r (ml)	Hausner ratio	Carr's index
Ratio 1	3.9	4	3	3	1.33	25
	3.9		3.1			
	3.8		3.2			
	3.9		3.2			
	3.9		3.4			
Ratio 2	3.1	3.3	2.8	2.5	1.32	24.24
	3.3		2.5			
	3.3		2.7			
	3.2		2.5			
	3.1		2.8			
Ratio 3	3.1	3.1	3.1	3.1	1.3	22.5
	3		3.2			
	2.9		3.2			
	2.8		3.3			
	3		3.2			
Ratio 4	3.5	3.6	3	2.8	1.29	22.22
	3.2		2.9			
	3.6		2.8			
	3.4		2.8			
	3.5		2.9			
Ratio 5	3.5	3.6	3	2.9	1.27	19.44
	3.6		2.9			
	3.2		3			
	3.3		2.9			
	3.4		2.9			

The angle of repose of Propranolol formula 4 was calculated by their cone height and radius

which were measured five times and then the average value was taken. The observed value is given below:

Table 4.24: Calculation of Angle of repose for Propranolol formula 4

Ratio	Height (h) cm	Avg. Height (h) cm	Radius (r) cm	Average Radius (r)cm	Angle of Repose
Ratio 1	1	1.08	1.45	1.475	36.25
	1.1		1.3		
	1.1		1.46		
	1.1		1.475		
	1.1		1.48		
Ratio 2	1	1.06	1.62	1.5165	34.95
	1		1.45		
	1.1		1.475		
	1.1		1.5375		
	1.1		1.5		
Ratio 3	1	.9	1.3625	1.39	32.92
	.9		1.35		
	1		1.3625		
	.8		1.4125		
	.8		1.4625		
Ratio 4	.9	.88	1.5125	1.5025	29.39
	.9		1.5		
	.9		1.5		
	.9		1.525		
	.8		1.475		
Ratio 5	.9	.84	1.5875	1.545	28.53
	.9		1.5		
	.8		1.5625		
	.8		1.5375		
	.8		1.5375		

4.2 Comparison shown using graph among 3 types (excipients, amlodipine, propranolol) of formulations (f1, f2, f3, f4) on the basis of Carr's index, Hausner ratio, and Angle of repose

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

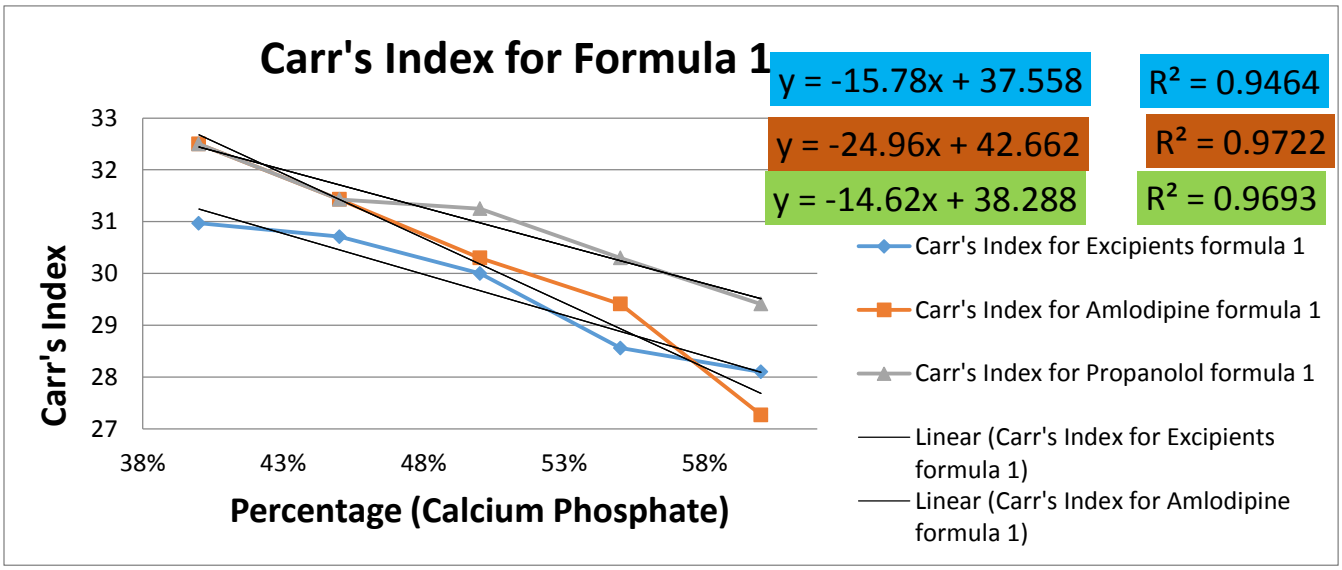


Figure 4.1: A percentage ratio of calcium phosphate versus Carr's Index graph

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

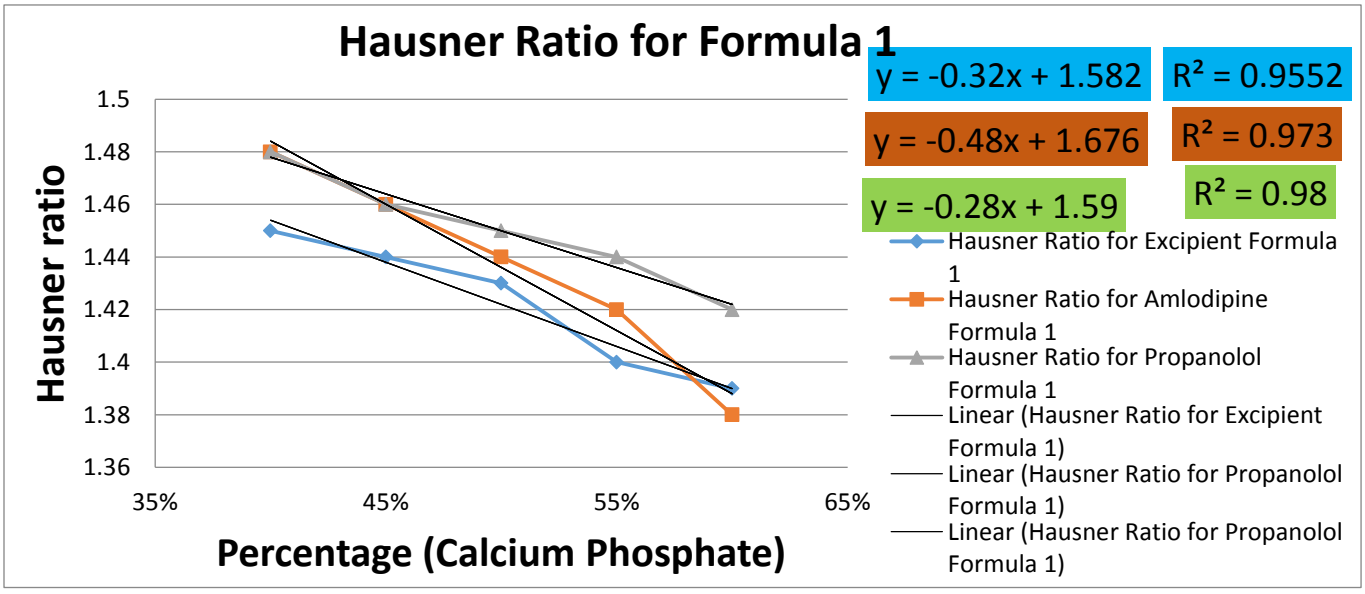


Figure 4.2: A percentage ratio of calcium phosphate versus Hausner ratio graph

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

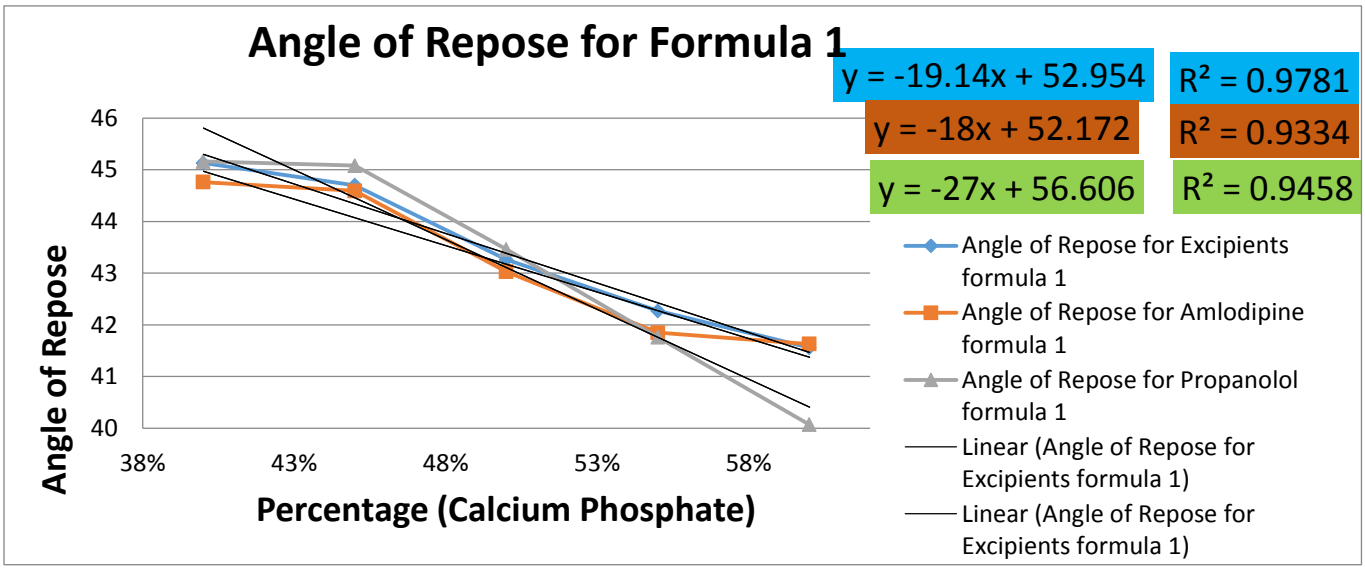


Figure 4.3: A percentage ratio of calcium phosphate versus Angle of repose graph

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

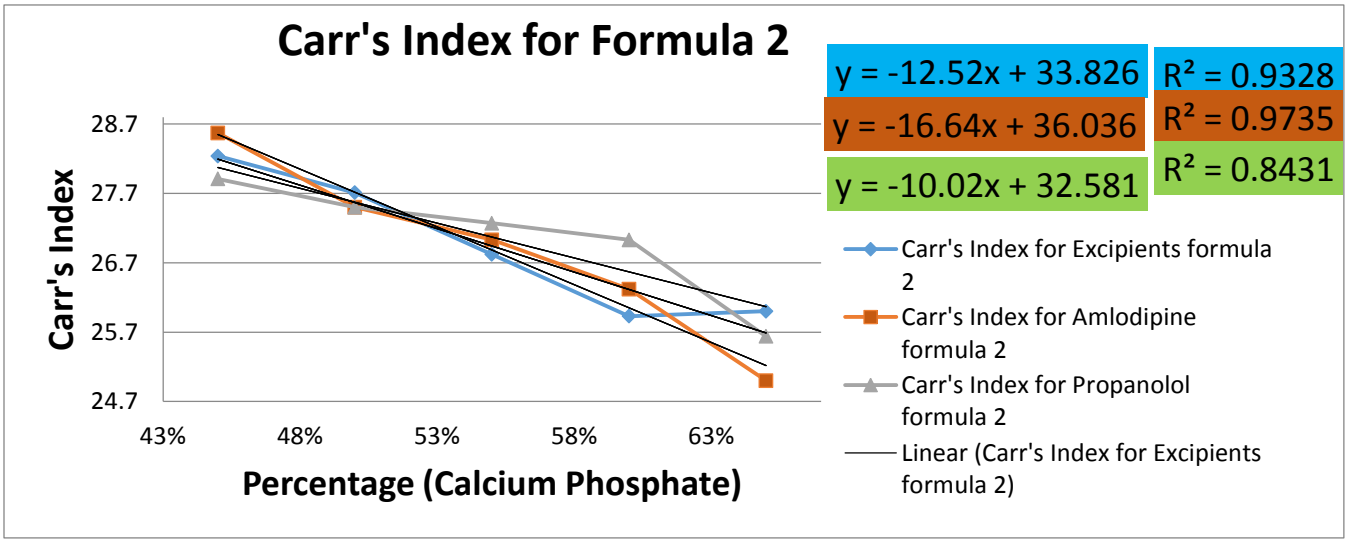


Figure 4.4: A percentage ratio of calcium phosphate versus Carr's Index graph

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

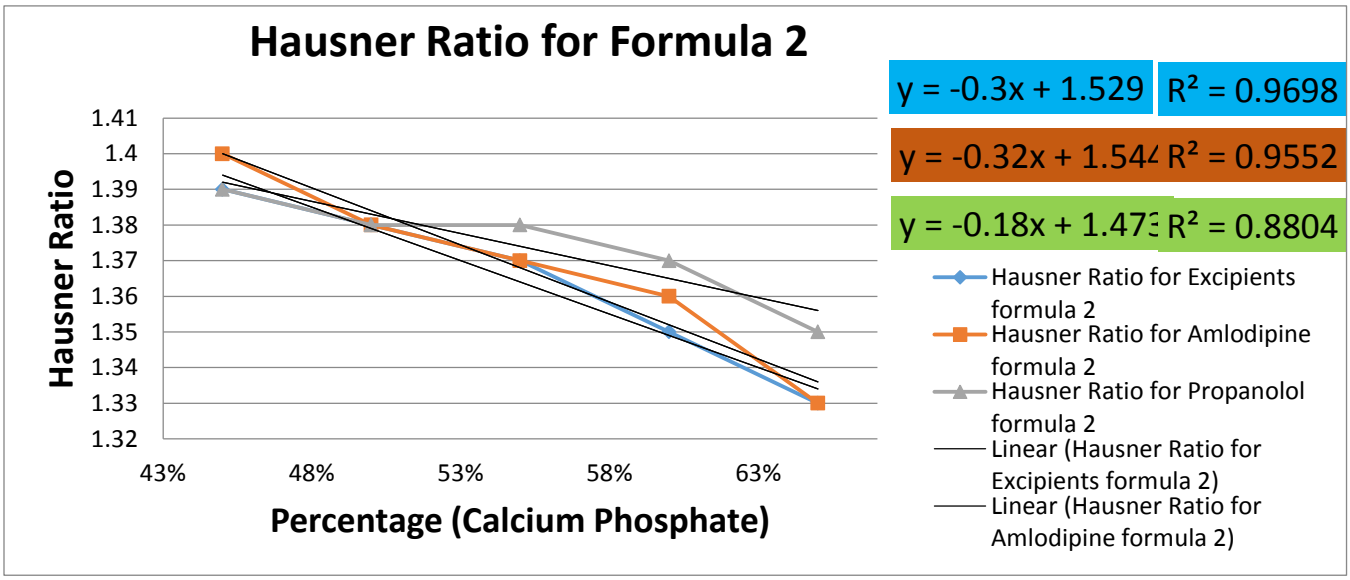


Figure 4.5: A percentage ratio of calcium phosphate versus Hausner ratio graph

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

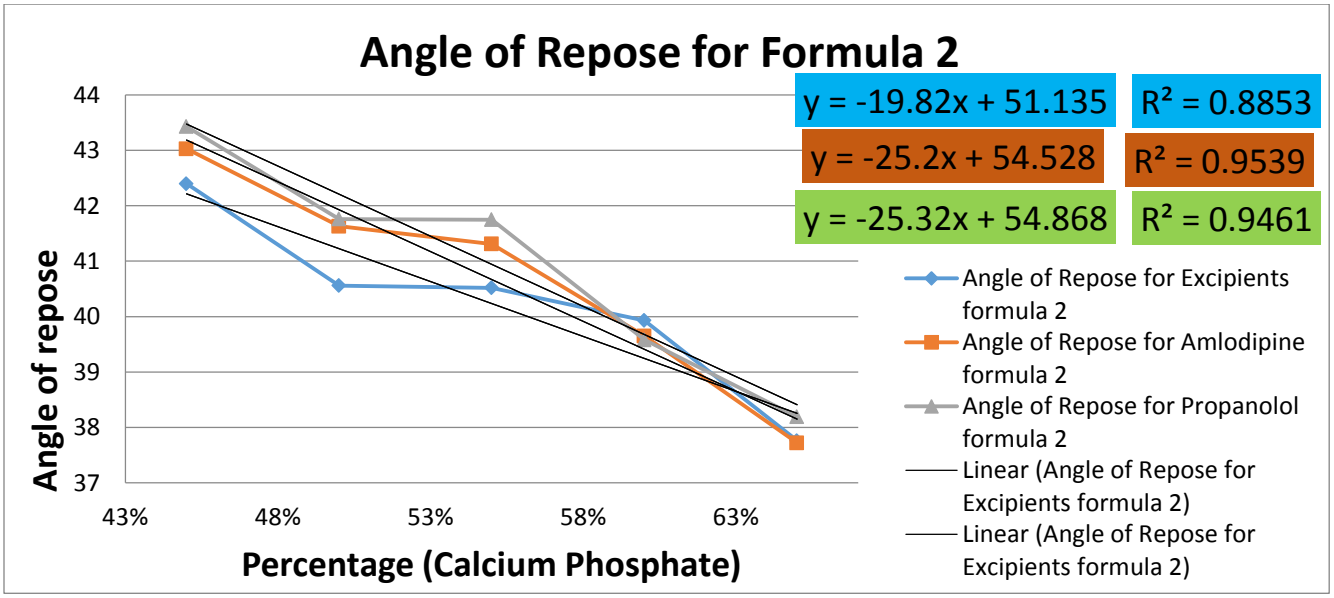


Figure 4.6: A percentage ratio of calcium phosphate versus Angle of repose graph

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

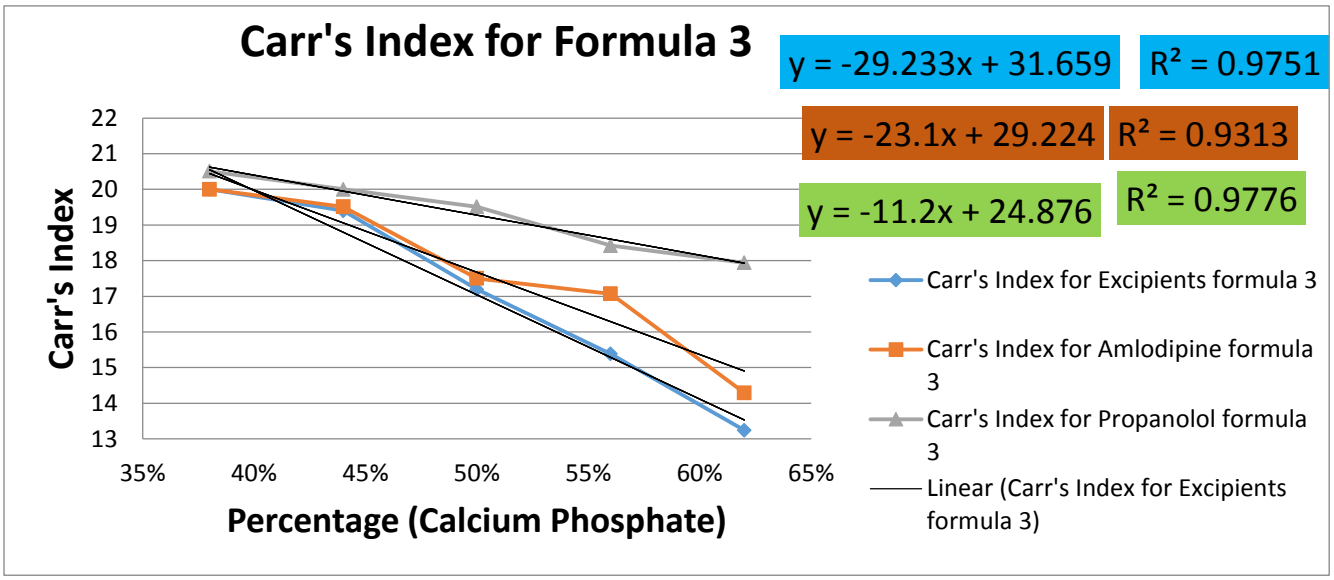


Figure 4.7: A percentage ratio of calcium phosphate versus Carr's Index graph

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

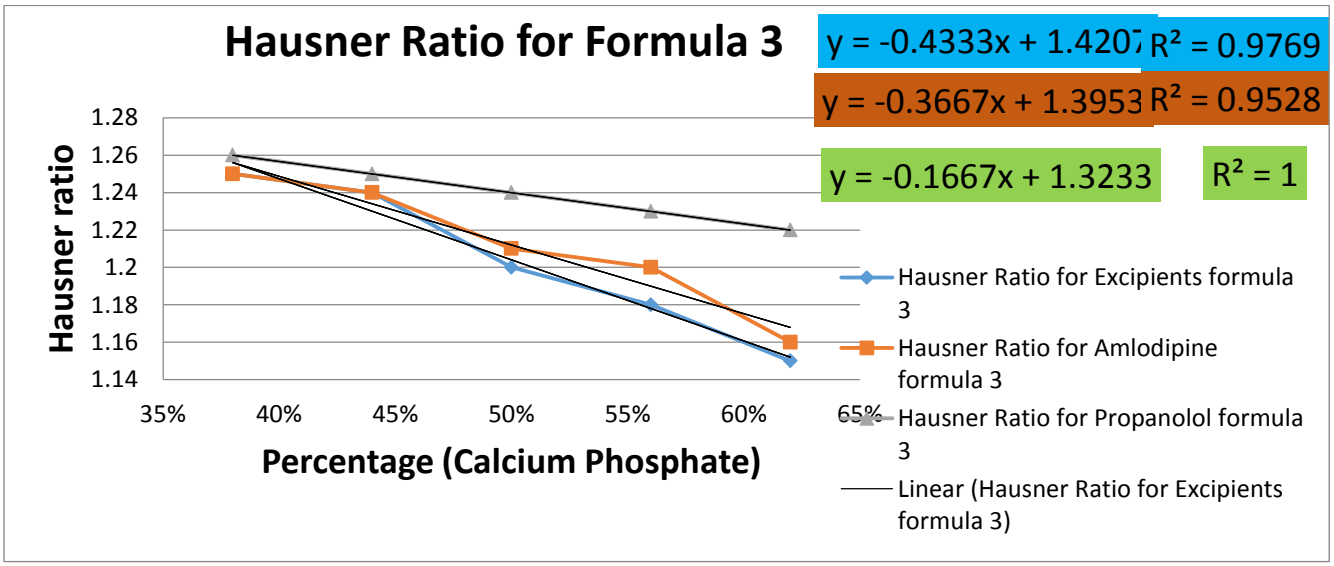


Figure 4.8: A percentage ratio of calcium phosphate versus Hausner ratio graph

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

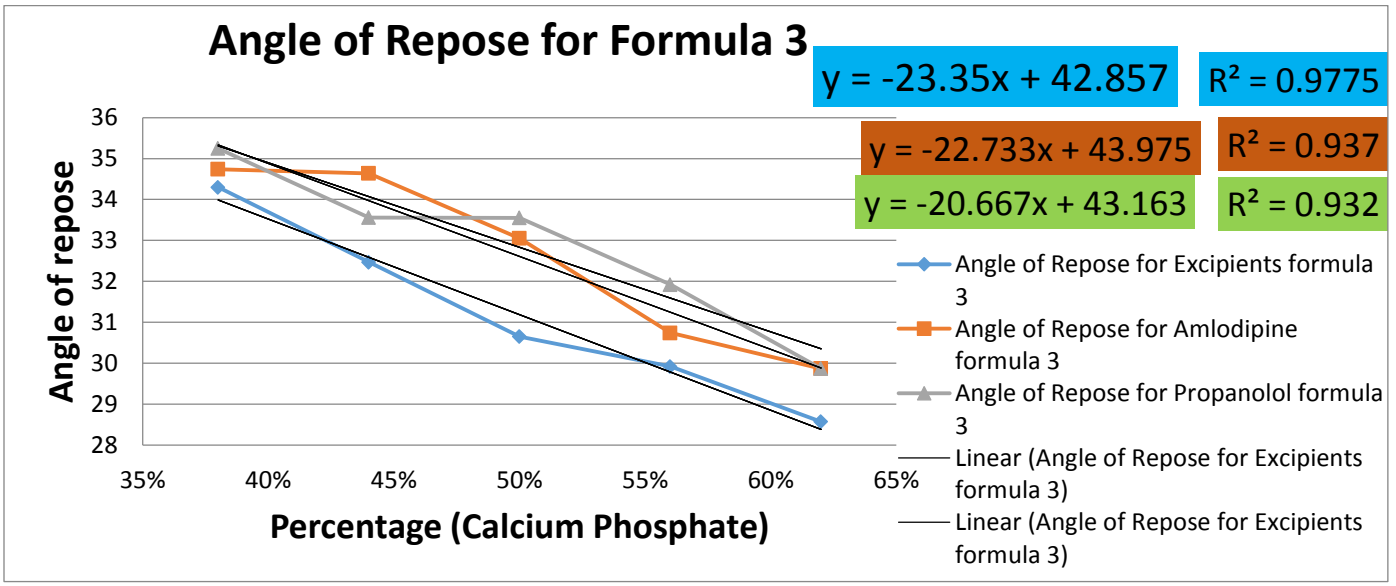


Figure 4.9: A percentage ratio of calcium phosphate versus Angle of repose graph

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

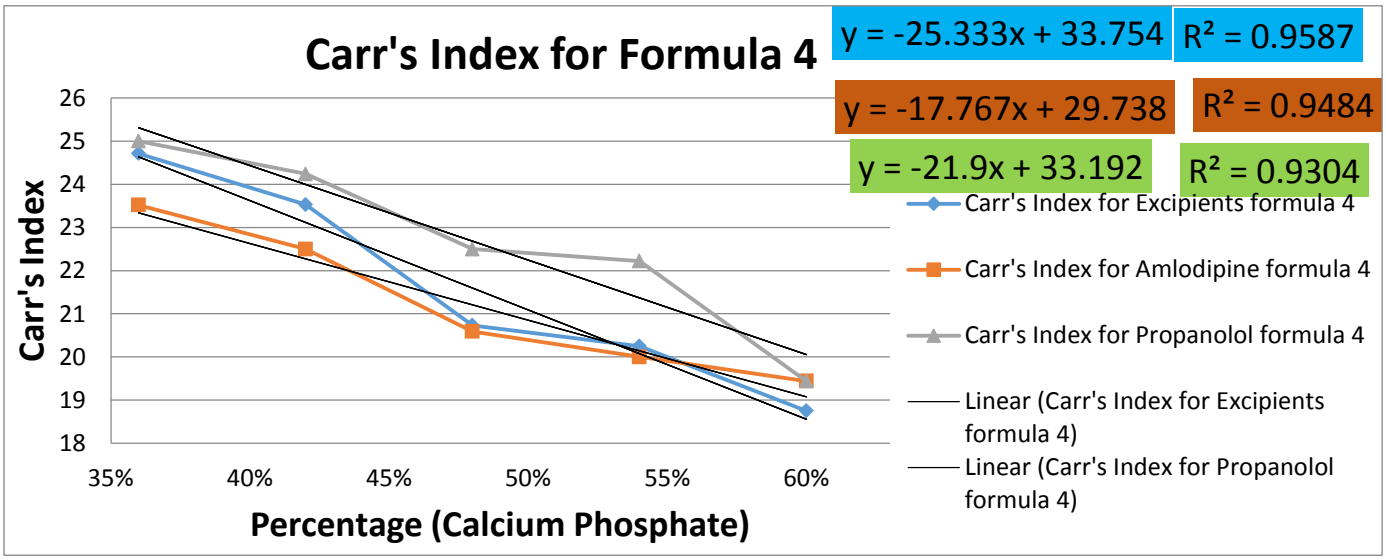


Figure 4.10: A percentage ratio of calcium phosphate versus Carr's Index graph

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

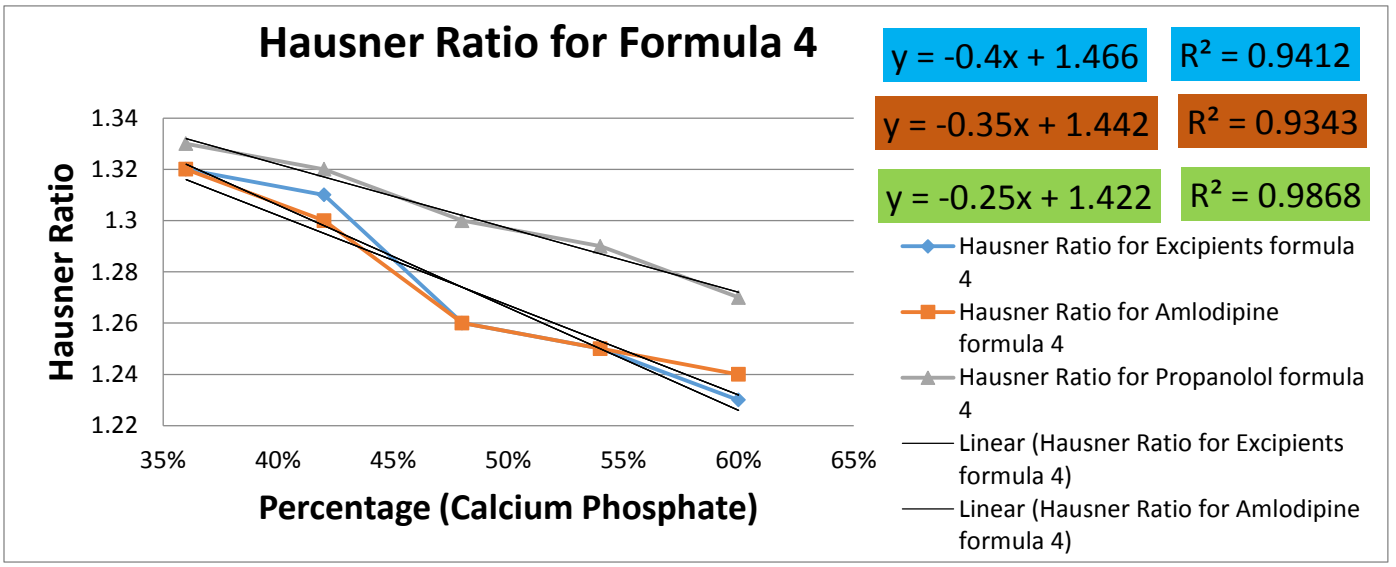


Figure 4.11: A percentage ratio of calcium phosphate versus Hausner ratio graph

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

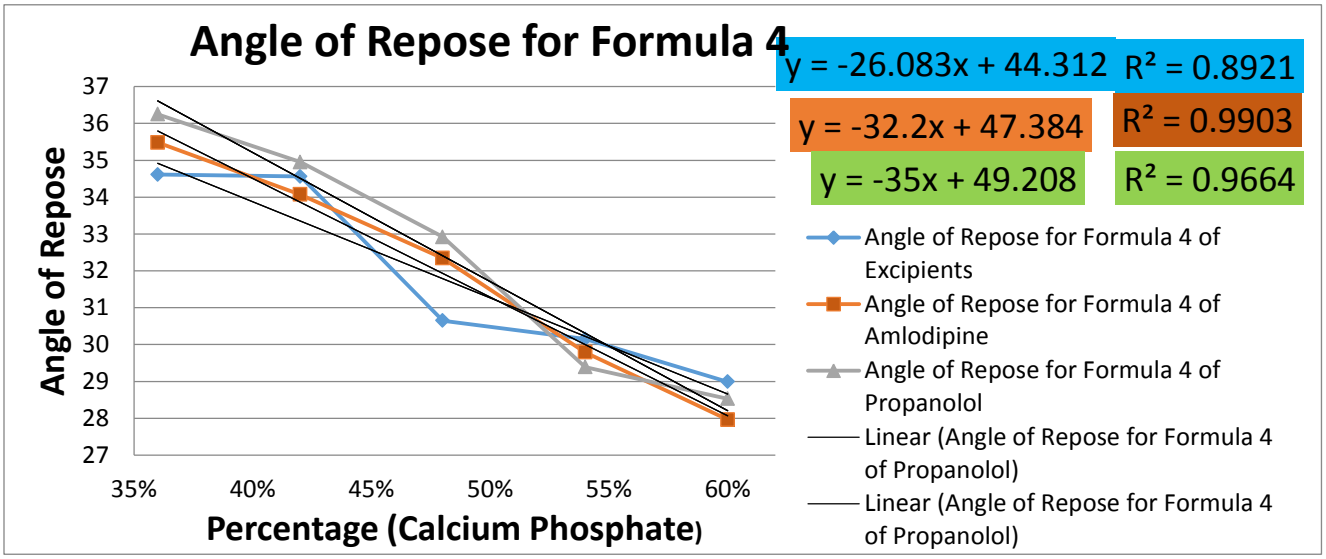


Figure 4.12: A percentage ratio of calcium phosphate versus Angle of repose graph

Table 4.25: Carr's Index equations and best percentage with flow property

Formula	Equation and regression value	Best percentage of Ca phosphate	Flow property according to USP29
F1	y = -15.78x + 37.558 , R^2 = 0.9464	60%	Poor
F1	y = -24.96x + 42.662 , R^2 = 0.9722	60%	Very poor
F1	y = -14.62x + 38.288 R^2 = 0.9693	60%	Very poor
F2	y = -12.52x + 33.826 , R^2 = 0.9328	65%	Passable
F2	y = -16.64x + 36.036 , R^2 = 0.9735	65%	Passable
F2	y = -10.02x + 32.581 , R^2 = 0.8431	65%	Passable
F3	y = -29.233x +31.659 , R^2 = 0.9751	62%	Good
F3	y = -11.2x + 24.876 , R^2 = 0.9313	62%	Good
F3	y = -11.2x + 24.876 , R^2 = 0.9776	62%	Fair
F4	y = -25.333x +33.754 , R^2 = 0.9587	60%	Fair
F4	y = -17.767x +29.738 , R^2 = 0.9484	60%	Fair
F4	y = -21.9x + 33.192 , R^2 = 0.9304	60%	Fair

Table 4.26:Hausner Ratio equations and best percentage with flow property

Formula	Equation and regression value	Best percentage of Ca phosphate	Flow property according to USP29
F1	y = -0.32x + 1.582, R^2 = 0.9552	60%	Poor
F1	y = -0.48x + 1.676 , R^2 = 0.973	60%	Poor
F1	y = -0.28x + 1.59 , R^2 = 0.98	60%	Poor
F2	y = -0.3x + 1.529 , R^2 = 0.9698	65%	Poor
F2	y = -0.32x + 1.544 ,R^2 = 0.9552	65%	Poor
F2	y = -0.18x + 1.473 , R^2 = 0.8804	65%	Poor
F3	y = -0.4333x + 1.4207 , R^2 = 0.9769	62%	Good
F3	y = -0.3667x + 1.3953 , R^2 = 0.9528	62%	Good
F3	y = -0.1667x + 1.3233 , R^2=1	62%	Fair
F4	y = -0.4x + 1.466 , R^2 = 0.9412	60%	Fair
F4	y = -0.35x + 1.442 , R^2 = 0.9343	60%	Passable
F4	y = -0.25x + 1.422 , R^2 = 0.9868	60%	Passable

Table4.27: Angle of Repose equations and best percentage with flow property

Formula	Equation and regression value	Best percentage of Ca phosphate	Flow property according to USP29
F1	y = -19.14x + 52.954 , R^2 = 0.9781	60%	Passable
F1	y = -18x + 52.172 , R^2 = 0.9334	60%	Passable
F1	y = -27x + 56.606 , R^2 = 0.9458	60%	Fair
F2	y = -19.82x + 51.135 , R^2 = 0.8853	65%	Fair
F2	y = -25.2x + 54.528 , R^2 = 0.9539	65%	Fair
F2	y = -25.32x + 54.868, R^2 = 0.9461	65%	Fair
F3	y = -23.35x + 42.857 , R^2 = 0.9775	62%	Excellent
F3	y = -22.733x + 43.975 , R^2 = 0.937	62%	Excellent
F3	y = -20.667x + 43.163 , R^2 = 0.932	62%	Excellent
F4	y = -26.083x + 44.312 , R^2 = 0.8921	60%	Excellent
F4	y = -32.2x + 47.384 . R^2 = 0.9903	60%	Excellent
F4	y = -35x + 49.208 , R^2 = 0.9664	60%	Excellent

So the result can be summarized as follows:

Table 5.1 Flow property of F1 and F2 according to Hausner ratio

F1	Hausner ratio range	Flow property	F2	Hausner ratio range	Flow property
Excipients	1.45-1.38	Poor	Excipients	1.37-1.35	Poor
Amlodipine	1.48-1.38	Very poor-Poor	Amlodipine	1.4-1.35	Very poor-Poor
Propranolol	1.48-1.42	Very poor-Poor	Propranolol	1.39-1.35	Poor

Table 5.2 Flow property of F3 and F4 according to Hausner ratio

F3	Hausner ratio range	Flow property	F4	Hausner ratio range	Flow property
Excipients	1.25-1.15	Fair-Good	Excipients	1.32-1.23	Passable-Fair
Amlodipine	1.25-1.16	Fair-Good	Amlodipine	1.32-1.27	Passable
Propranolol	1.26-1.22	Fair	Propranolol	1.33-1.27	Passable

Table 5.3 Flow property of F1 and F2 according to Carr's index

F1	Carr's index range	Flow property	F2	Carr's index range	Flow property
Excipients	30.97-28.1	Poor	Excipients	28.63-25.93	Poor-Passable
Amlodipine	32.5-27.27	Poor-Very poor	Amlodipine	28.57-25.64	Poor-Passable
Propranolol	32.5-29.41	Poor-Very poor	Propranolol	27.91-25.64	Poor-Passable

Table 5.4 Flow property of F3 and F4 according to Carr's index

F3	Carr's index range	Flow property	F4	Carr's index range	Flow property
Excipients	20-13.24	Fair-Good	Excipients	24.71-18.75	Passable- Fair
Amlodipine	20-14.29	Fair-Good	Amlodipine	23.52-19.44	Passable- Fair
Propranolol	20.51-17.94	Fair	Propranolol	25-19.44	Passable- Fair

Table 5.5 Flow property of F1 and F2 according to angle of repose

F1	Angle of repose range	Flow property	F2	Angle of repose range	Flow property
Excipients	45.13-41.56	Passable	Excipients	42.4-37.76	Passable- Fair
Amlodipine	44.76-41.63	Passable	Amlodipine	43.03-37.72	Passable- Fair
Propranolol	45.16-40.07	Passable- Fair	Propranolol	43.43-38.19	Passable- Fair

Table 5.6 Flow property of F3 and F4 according to angle of repose

F3	Angle of repose range	Flow property	F4	Angle of repose range	Flow property
Excipients	34.3-28.56	Fair-Excellent	Excipients	34.61-28.99	Fair-Excellent
Amlodipine	34.74-29.87	Fair-Excellent	Amlodipine	35.48-27.96	Fair-Excellent
Propranolol	35.25-29.87	Fair-Excellent	Propranolol	36.25-28.53	Fair-Excellent

In this research project, I have determined flow characteristic of some groups of excipients and APIs. Each of the combinations contained a certain formula prepared by 4 types of excipients and a diluent. Diluents were used in various amounts with the formulas to check its effect on the existing formula. For the most obvious property of diluent, that, it accelerates powder flow, the

existing formulas have performed better with the addition of increasing amount of diluents. Almost each of the combinations have shown average results, others have shown poor to very poor results according to the use of excipients. The project might have gone through any environmental imbalance, or human error, as all of this assessments was conducted manually and there was lack of expertise.

Chapter Five

DISCUSSION

5.1 Hausner ratio of F1 and F2

From table 5.1,

- In F1 where I used only the excipient batch and fixed amount of diluent showed poor result for Hausner ratio. But with the increasing amount of diluent the ratio also increased. Similar results were seen for F2 as well.
- While I mixed Amlodipine in F1 and F2 in a fixed amount, both of the formulations showed the result in a range of very poor to poor.
- While added Propranolol, the F1 showed very poor result but F2 showed poor range of Hausner ratio.

5.2 Hausner ratio of F3 and F4

From table 5.2,

- F3 Excipients batch showed fair to good result range of Hausner ratio. But F4 showed passable to fair range. It is due to the diluent percentage mainly.
- F3 Amlodipine batch showed fair to good result as well but F4 amlodipine batch showed passable result.
- F3 Propranolol group showed fair range but F4 showed passable range of Hausner ratio.

5.3 Carr's index of F1 and F2

From table 5.3,

- Carr's index of F1 excipient batch was poor and with addition of both APIs it worsen.
- Carr's index of F2 for all the batches remained in poor to passable range. That means it increased a little with the increasing amount of calcium phosphate and we can see the result being passable from poor.

5.4 Carr's index of F3 and F4

From table 5.4,

- F3 excipients batch showed fair to good range of Carr's index along with Amlodipine batch. But propranolol showed fair range.

- F4 showed passable to fair range for all excipients and API as well.

5.5 Angle of repose for F1 and F2

From table 5.5,

- F1 for excipients and Amlodipine showed passable range but propranolol showed passable to fair range of angle of repose.
- F2 showed passable to fair range of angle of repose for all excipients and APIs.

5.6 Angle of repose for F3 and F4

From table 5.6

- All the results for Angle of repose for both F3 and F4 showed ranges that lie between fair to excellent. That means the flow properties according to angle of repose are excellent in these two formulations.

5.7 Required amount of calcium phosphate for excellent Carr's Index value

Equation from the graph can be used to acquire Carr's index value within excellent range that is 10 according to USP. From that equation, the value of x can be determined that denotes the amount of Calcium phosphate. For example, F1 formula is shown below:

Table5.7 Required amount of calcium phosphate for excellent Carr's Index value

Formula	Equation and regression value	Required Ca phosphate (%)	Carr's Index value (excellent)
F1	$y = -15.78x + 37.558$, $R^2 = 0.9464$	58.33	10
F1	$y = -24.96x + 42.662$, $R^2 = 0.9722$	43.66	10
F1	$y = -14.62x + 38.288$ $R^2 = 0.9693$	64.33	10

5.8 Required amount of calcium phosphate for excellent Hausner ratio value

Equation from the graph can be used to acquire Hausner ratio value within excellent range that is according to USP. From that equation, the value of x can be determined that denotes the amount of Calcium phosphate. For example, F1 formula is shown below:

Table 5.8 Required amount of calcium phosphate for excellent Hausner ratio value

Formula	**Equation and regression value**	**Required Ca phosphate (%)**	**Hausner ratio (excellent)**
F1	$y = -0.32x + 1.582$, $R^2 = 0.9552$	60.67	1
F1	$y = -0.48x + 1.676$, $R^2 = 0.973$	47	1
F1	$y = -0.28x + 1.59$, $R^2 = 0.98$	70.33	1

5.9 Required amount of calcium phosphate for excellent Angle of Repose value

Equation from the graph can be used to acquire Angle of Repose value within excellent range that is according to USP. From that equation, the value of x can be determined that denotes the amount of Calcium phosphate. For example, F1 formula is shown below**:**

Table 5.9 Required amount of calcium phosphate for excellent Angle of Repose value

Formula	**Equation and regression value**	**Required Ca phosphate (%)**	**Angle of Repose(excellent) (°)**
F1	$y = -19.14x + 52.954$, $R^2 = 0.9781$	48.67	25
F1	$y = -18x + 52.172$, $R^2 = 0.9334$	50.33	25
F1	$y = -27x + 56.606$, $R^2 = 0.9458$	34	25

From this research it is seen that F1 and F2 didn't show good flow properties which is hazardous for solid dosage form manufacture. So it is better not to use those combinations of formula. But it has been seen that with the increasing amount of diluent calcium phosphate, the flow property increased but not in a reasonable extent in case of F1 and F2. On the contrary, F3 and F4 showed passable to excellent ranges of result in these flow property measurements. The graphs also show that the formulation F3 gives the best flow properties among all. F3 and F4 both gives good flow property but F3 is best set of excipients and that is justified with 2 APIs as well.

The graphs indicates linearity in result which means that the increasing amount of calcium phosphate improves the flow property of powder. Though diluent is used to fill the drug in a suitable dosage form, our study has been proved that this specific diluent can improve the flow property. The increasing flow property with increasing Calcium phosphate amount can be a consequence due to the glidant property of calcium phosphate. It also works as binder which is useful for direct compression. The equations I have developed in this project can be used to determine the amount of diluent used to have the best powder flow. Thus the new drug development will have an ease for research and existing drugs' manufacture can be improved.

Chapter Six

CONCLUSION

6.1 Conclusion

Excipients serves a variety of application and uses from the process of manufacturing of drugs to bioavailability throughout the human body. For the process of tableting, the ingredients flowability is an important sector as powders have to pass through the hopper to the punching dyes. So the measurement of powder flow property is very necessary for any pharmaceutical industry or research sector. The study was conducted to observe the flow characteristics of different types of excipients alone with diluent Calcium phosphate in a definite amount of percentage and with APIs as well. It can be stated that variation in amounts of excipients in the mixture showed a variation in the powder flow characteristics. It is also true that due to some lacking during the research work the result is deviated little. Overall this research work will be beneficial in formulation development of new drug product as well as this research work will be advantageous for Research & Development department of pharmaceutical company. We can see in the literatures that no such kind of study is conducted so far. This study will minimize the time for development of new drugs and also it is economical so unnecessary assessments will be avoided if this study is followed. This project can also help improving the existing drugs with poor powder flow property which is hazardous for manufacturing and also for bioavailability. This prediction of good powder flow property will be beneficial for PFS, PFI, powder for encapsulation, powder for dry granulation, and most importantly for direct compression.

Chapter Seven

Reference

7.1 References

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