Determination of variation in flow property of different formulas of CMC along with amlodipine and propranolol

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

DECLARATION BY THE CANDIDATE

I, Rabeya Sultana Meem, hereby declare that the dissertation entitled "Determination of variation in flow property of different formulas of CMC along with amlodipine and propranolol", submitted by me to the Department of Pharmacy, East West University, in the partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Honors) with original research work carried out by me under the supervision and guidance of Mohammad Faisal Bin Karim, Lecturer, Department of Pharmacy, East West University, Dhaka.

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Certificate by Supervisors

This is to certify that the dissertation entitled “Determination of variation in flow property of different formulas CMC 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 Rabeya Sultana Meem (ID: 2011-3-70-021) under our guidance and supervision and that no part of the research has been submitted for any other degree. We further certify that all the sources of information and laboratory facilities availed of in this connection is duly acknowledged.

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This is to certified that the dissertation entitled “Determination of variation in flow property of different formulas of CMC 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 Rabeya Sultana Meem (ID: 2011-3-70-021) under our guidance and supervision of Mohammad Faisal Bin Karim, Lecturer, Department of Pharmacy, East West University, Dhaka.

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ABSTRACT

Flow property is very important in the pharmaceutical industry for the manufacturing process such as blending, tablet compression, capsule filling, transportation, and in scale-up operation. The purpose of this research work was to find out that ratio of pharmaceutical excipients in a mixture that will provide maximum or minimum flow property. The equations that i proposed will be helpful for determining the flow property of new solid drug formulations. I had measured several parameters, such as, bulk volume, tapped volume, Carr's index, Hausner ratio and angle of repose for different mixture of same pharmaceutical excipients. We had done this for different mixtures of different excipients with different ratios of CMC to determine different equations. I evaluated the laboratory experimental data to determine several specific equations (y= mx + c) for particular mixtures of specific pharmaceutical excipients. After doing the research I found that at the lowest amount of CMC I used in set 1 (3%:97%) with amlodipine gave best result and at the ratio (30%:70%) gave very poor result with amlodipine. For propranolol I got the best result when CMC was lower at the ratio (3%:97%) and got poor result when CMC was higher at the ratio (30%:70%). For a new solid drug formulations flow property of pharmaceutical excipients can be predicted and measured by these equations.

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

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Chapter 1:

Introduction

1.1INTRODUCTION

Powder flow characteristic is an important parameter during drug manufacturing process. The object of this experiment was to determine the variation of flow property of different set of ratio of excipients. In this research flow characteristics of mixture of excipients were determined using individual excipients of different classes of excipients. At first the most important classes of excipients were chosen and then widely used excipients from these classes are listed. Then flow characteristics of excipients were measured by using several parameters, such as, bulk density, tapped density, Carr's index, Hausner ratio and angle of repose for different mixture of same pharmaceutical excipients but in different ratio, and were able to resolve an equation. (Shah, Tawakkul and Khan, 2008)

In any formulation apart from active ingredients, inactive excipients play very important role. Pharmaceutical excipients are substances other than the pharmacologically active drug or prodrug which are included in the manufacturing process or are contained in a finished pharmaceutical product dosage form. So it is necessary to check the physicochemical properties of pharmaceutical excipients. For a definite pharmaceutical formulation, choosing the appropriate combination of excipients which can serve the required quality is essential. For this reason measurement of flow properties of powders is considered mandatory in any tablet or capsule formulation. (Young, 2013)

The purpose of this research project was to find out the variable flow properties of any set of excipients from plotting a standard curve of a particular combination of excipients. For accurate result, the experiments were done three times and all the guidelines were followed.(Young, 2013)

1.2 POWDER FLOW

The pervasive use of powders in the pharmaceutical industry has created a variety of methods for symbolizing powder flow .Not surprisingly, scores of references appear in the pharmaceutical literature, trying to relate the various measures of powder flow to manufacturing properties. The development of such a variety of test methods was impossible to avoid and the behaviors of powder flow properties are many-sided and this complicates the effort to characterize the powder flow. The object of this part is to review the methods for characterizing powder flow. (Pharmacopeia.cn, 2016)

1.2.1 Definition of Powder Flow: Powder flow is the flow ability of powder that means the ability of a powder to flow. By this definition, flow ability is sometimes thought of as a one-dimensional characteristic of a powder, by which powders can be ranked on a sliding scale from "free-flowing" to "non-flowing". The inability to achieve reliable powder flow during manufacturing process of solid dosage forms of any drug can have a significant adverse effect on the total process, whether from manufacture to the release of a product to market. Production costs can be significantly higher than anticipated due to interference required on the part of operators, low yield or unplanned process redesign.(Pharmacopeia.cn, 2016)

1.2.2 Importance of learning accurate flow property: It is very important to know the flow property of powder to check 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. Same powder can flow well in hopper but poor in other.so it is very important to know the flow property of powder. It is very important in developing new product and formulation, in quality improving and in reducing the cost.

In developing new product: 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.

In 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.

In lowering the cost: 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. (Young, 2013)

1.2.3 Factors Affecting Powder Flow Properties: There are several factors which are affecting flow properties of powder. Such as-

-Particle size

-Size distribution

-Shape

-Surface area(User, 2016)

1.2.4 Methods Of powder flow: There are several methods which are used to determine the powder flow. They are- angle of repose, compressibility index or hausner ratio, flow rate on orifice and shear cell.(Shah, Tawakkul and Khan, 2008)

1.2.5 Angle of repose: It is determined by using a funnel attached with a stand. The individual powder excipient or mixture of powder excipients are freely passed over the funnel and after that using an equation, we determined the values of angle of repose of respective individual powder excipient or mixtures of powder excipients. The values of angle of repose indicate the respective flow characteristic of individual powder excipient or mixture of powder excipients.(Young, 2015)

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

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

Where, h = height of the powder cone from the base; r = radius of the conical pile.(Pharmacopeia.cn, 2016)

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Accepted value of angle of repose:

Table 1.1 Flow Properties and Corresponding (Angles of Repose): (Pharmacopeia.cn, 2016)

Flow Property	*Angle of Repose (degrees)*
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55

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).

1.2.6 Carr's index or compressibility index and Hausner's ratio: They are another significant powder flow measuring parameters. They are calculated by using bulk volume and tapped volume of a certain amount of powder excipient in a measuring cylinder. These two parameters can also be determined by measuring bulk density and true density of a particular amount of any powder. In according to United States Pharmacopeia, although there are some variations in the determining of the Carr's index and Hausner's ratio, the basic procedure is to measure the unsettled bulk volume and the final tapped volume of the powder after tapping the material until no further volume changes occur. The compressibility index and the Hausner'sratio are calculated as follow:

$$\textbf{Carr's Compressibility Index} = 100 \times \left(\frac{Bulk\ volume\ -\ Tapped\ volume}{Bulk\ volume}\right)$$

$$\textbf{Hausner's Ratio} = \left(\frac{Bulk\ volume}{Tapped\ volume}\right)$$

(Young, 2015)

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

$$\textit{Carr's Compressibility Index} = 100 \times \left(\frac{\textit{True density} - \textit{Bulk density}}{\textit{True density}}\right)$$

$$\textit{Hausner's Ratio} = \left(\frac{\textit{True density}}{\textit{Bulk density}}\right)$$

(Young, 2015)

1.2.7 Generally accepted value of curr's index and Hausner's ratio:

Table 1.2 Scale of Nature of flow in Carr' Index and Hausner's Ratio Values: (Pharmacopeia.cn, 2015)

Carr's Index (%)	Flow Character	Hausner Ratio
≤10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

1.2.8 Factors affecting Carr's Index and Hausner Ratio:

There are some several factors affecting Carr's Index and Hausner Ratio. They are:

- 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

In this research individual flow characteristics of an excipient and flow characteristics of that excipient along with other excipients was determined by which we can chose the best excipients for pharmaceutical products. (Pharmacopeia.cn, 2015)

1.3 Pharmaceutical Excipients

1.3.1 Definition: The word excipients derived from the Latin excipere, meaning 'to except', which is simply explained as 'other than'. Pharmaceutical excipients are basically everything other than the active pharmaceutical ingredient. Ideally, excipients should be inert, however, recent reports of adverse reactions have suggested otherwise.(Australianprescriber.com, 2016)

Pharmaceutical excipients are substances other than the pharmacologically active drug or prodrug which are included in the manufacturing process or are contained in a finished pharmaceutical product dosage form.(Australianprescriber.com, 2016)

1.3.2 Function of Excipients: Today, 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. They may also assist in product identification and enhance the overall safety or function of the product during storage or use.(Australianprescriber.com, 2016)

Thousands of different excipients are used in medicines and make up, on average, about 90% of each product. They represent a market value of €3 billion (almost $4 billion) accounting for 0.5% of the total pharmaceutical market according to industry experts.(Australianprescriber.com, 2016)

1.3.3 Common excipients used in tablets

The list of purposes for which excipients are used, as defined in international pharmacopoeias, is extremely long. Many excipients have more than one use, which can be an advantage since it reduces the number of excipients needed and minimizes the risk of interactions between them. Tablets are the most widely used dosage form. Their manufacture can be a complex process and considerable ingenuity and formulation expertise are required to produce a product that will be stable during storage, transport and handling, yet will release its active pharmaceutical ingredient as required once ingested. Commonly used excipients can be categorized as below:

- Diluents
- Disintegrants
- Binders
- Lubricants
- Glidants
- Preservatives
- Stabilizers
- Colorants
- Sweeteners. (Haywood and Glass, 2011)

1.3.4 Diluents or Fillers:

Functions of diluents

Bulking agent– E.g. to make a tablet weight practical for the patient: minimum tablet weight is typically ~50mg. Actual API doses can be as low as ~20µg, e.g. for oral steroids.

Compression aid – Deforms and/or fragments readily to facilitate robust bonding in tablet compacts, e.g. microcrystalline cellulose.

Good bulk powder flow….diluents have a strong influence – Good flow of bulk powders is very important in designing a robust commercial tablet product.

Favoured combinations: Lactose is an excellent choice of filler in many respects but can exhibit poor flow characteristics, so is often combined with free-flowing microcrystalline cellulose in wet granulation formulations. (Patel, Shah and Upadhyay, 2015)

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Examples of Diluents:

lactose, lactose anhydrous, lactose spray dried, directly compressible starch, hydrolyzed starch, MCC, other cellulose derivatives, dibasic calcium phosphate dihydrate, mannitol, sorbitol, sucrose, calcium sulfate dehydrate, dextrose. (Anon, 2016).

1.3.5 Disintegrants:

Function of Disintegrants:

As an aid to de-aggregation of solid dosage forms. Disintegrants causerapid break up (disintegration) of solid dosage forms upon exposure tomoisture.

Generally, disintegration is viewed as the first stage in the dissolutionprocess, although dissolution does occur simultaneously with disintegration.

Mode of action:

– In many cases water uptake alone will cause disintegration, by rupturing theintra-particle cohesive forces that hold the tablet together and resulting insubsequent disintegration.

– If swelling occurs simultaneously with water uptake, the channels forpenetration are widened by physical rupture and the penetration rate of waterinto the dosage form increased.(TheFreeDictionary.com, 2016)

Examples of Disintegrants:

Croscarmellose sodium, sodium starch glycolate, polyvinyl pyrrolidone and crospovidone are the most commonly used super disintegrants. (Anon, 2016)

1.3.6 Binders:

Function Of Binders:

Binders act as an adhesive to ‘bind together’ powders, granules andtablets to result in the necessary mechanical strength:

– As a dry powder with other excipients in dry granulation (roller compaction, slugging) or as anextra-granular excipient in a wet granulation tablet formulation.

– As a dry powder with other intra-granular excipients in wet granulation. When the granulatingfluid is added, the binder may dissolve partially or completely to then exhibit adhesive bindingproperties in helping granules to form.

– Most commonly in wet granulation, the binder is added already dissolved in the granulating fluidto enable a more effective and controllable granule formation.

– Water is the most common granulating fluid, very occasionally in a co-solvent system with, e.g.ethanol.

Examples of Binders:

– Dry binders: Pregelatinised starch, cross-linked PVP

– Solution binders: HPMC, PVP

– Soluble in water/ethanol mix: PVP. (Anon, 2016)

1.3.7 Lubricants:

Function of Lubricants:

Compression lubricants prevent adherence of granule/powder to punch die/faces and promote smooth ejection from the die after compaction:

– Magnesium stearate is by far the most extensively used tableting lubricant

– There are alternatives, e.g. stearic acid, sodium stearyl fumarate.

– Lubricants tend to be hydrophobic, so their levels (typically 0.3 – 2%) need to beoptimized:

- Under-lubricated blends tend to flow poorly and show compression sticking problems

- Over-lubricated blends can adversely affect tablet hardness and dissolution rate

-Lubricants can also be used when compression isn’t involved,

e.g. – In powder blends for filling into capsules to prevent adherence of granule/powder toequipment’s surfaces.

– Coating the surface of multi-particulate dosage forms (including intermediate product)to inhibit agglomeration of individual particles

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Examples:

Any stearates, like magnesium, calcium, zinc, or sodium stearates, Sodium stearylfumarate, boric acid, sodium lauryl sulfate, stearic acid etc can be used as lubricant within direct compressible tablets. (Gohel, 2015)

1.3.8 Glidants*:*

Functions of Glidants:

Most commonly; colloidal silicon dioxide (traditionally, talc was used)

- Good bulk powder flow ability, is especially important during high speedprocessing

-Glidants improve flow by adhering to particles and so reducinginter-particulate friction

– Most common in dry powder formulations, e.g. direct compression tablets

– Can also be added to granules to improve flow prior to compression

–can get undesirable “flooding” if flow is too good

-Very low levels required (ca. <0.2%)

– Control can be challenging with blends sensitive to levels

-Very low bulk density (0.03 – 0.04g/cm3)

– Difficult to work with (very voluminous) – not a standard excipient, only added ifneeded

Examples of Glidants:

Talc is an ideal glidant to be used in this dosage form. Concentration of starch is common up to 10%, but should be limited otherwise it will worsen the flow of material. Besides colloidal silicon dioxide added at a typical level of 0.1% to 0.2% will improve the flow characteristics of a compression mix. (Anon, 2016)

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1.3.9 Other excipients:

Preservative:

They are typically use to prevent any kind of microbial growth informulation. Some typical preservatives used in pharmaceutical formulations are antioxidants like vitamin A, vitamin E, vitamin C, retinyl palmitate, and selenium, the amino acids cysteine and methionine,Citric acid and sodium citrate, synthetic preservatives like the parabens: methyl paraben and propyl paraben.(Wikipedia, 2016)

Stabilizers:

These are typically used, if necessary, to minimize pH dependent hydrolysis or oxidation depending on the requirement of the drug substance. To promote intimate contact of the drug with the stabilizer it is generally recommended to include the stabilizer in finely divided form at the pre-mix stage. (Anon, 2016)

Colorants: Colorants are added to the formulation in order to increase the patent compliance or for identification of the formulation. Usually the colorants are added in the form of insoluble powder or in the form as liquid in the granulation liquid. To obtain evenness of coloration in directly compressed formulations the use of insoluble pigments (aluminum lakes and iron oxides) is preferred. Inclusion at the premix stage can minimize “speckling” in the finished tablets. Alternatively the tablets can of course be film coated. (Wikipedia, 2016)

Surfactants: Wetting agents such as sodium lauryl sulphate may be included, especially if the drug substance is hydrophobic. (Anon, 2016)

Flavoring agents: 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. (Anon, 2016)

1.4 An overview of this research

In this research I have chosen to test the effect of different ratio of an individual disintegrant in a particular formulation of a direct compressible tablet. As active ingredients I used amlodipine and propranolol. As disintegrant I used carboxy methyl cellulose (CMC).Now let us know about this targeted excipient, and the probable changes in the existing tablet formulations those are followed by addition or removal of a disintegrant, and also the changes of its amount in the formula. (Young, 2015)

1.4.1 Definition of Disintegrant:

Disintegrating agents is a substance or mixture of substances added to tablets to facilitateits break up or disintegration. The active constituents must be released from the tablet asefficiently as possible to allow its rapid action. Hence the therapeutic action is based on theamount of drug released from the tablet, these disintegrants which allows rapid de-aggregation ofsolid in to solution and followed by which absorption of the drug takes place. Most of theconventional and in novel preparation the impact of disintegrants had given a new dosage formsuch as rapid disintegrating tablets and mouth dissolving tablets. By fair choice of thedisintegrating agents which has a greater impact in the final formulation to enhance the drug bioavailability.(TheFreeDictionary.com, 2016)

1.4.2 Ideal Characteristics of Disintegrants:

1. Poor solubility

2. Poor gel formation

3. Good hydration capacity

4. Good molding and flow properties

5. No tendency to form complexes with the drugs.. (Anon, 2016)

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1.4.3Method of addition of disintegrants:

Disintegrants are essentially added to tablet granulation for causing the compressed tabletto break or disintegrate when placed in aqueous environment.

There are two methods of incorporating disintegrating agents into the tablet:

1. Internal Addition (Intra-granular)

2. External Addition (Extra-granular)

3. Partly Internal and External

In external addition method, the disintegrant is added to the sized granulation with mixing prior

to compression.

In Internal addition method, the disintegrant is mixed with other powders beforewetting the powder mixtures with the granulating fluid. Thus the disintegrant is incorporatedwithin the granules.

When these methods are used, part of disintegrant can be added internally andpart externally. This provides immediate disruption of the tablet into previously compressedgranules while the disintegrating agent within the granules produces further erosion of thegranules to the original powder particles. The two step method usually produces better and morecomplete disintegration than the usual method of adding the disintegrant to the granulation surfaceonly.. (Anon, 2016)

1.4.4 Mechanism of disintegration:

The mechanism by which the tablets are broken into small pieces and then produces ahomogeneous suspension is based on:

A. By Porosity and Capillary Action

B. By swelling

C. Because of heat of wetting

D. Due to disintegrating particle/particle repulsive forces

E. Due to deformation

F. Due to release of gases

G. By enzymatic action. (Anon, 2016)

A. Porosity and capillary action (wicking):

Effective disintegrants that do not swell are believed to impart their disintegrating actionthrough porosity and capillary action. Tablet porosity provides pathways for the penetration offluid into tablets. The disintegrant particles (with low cohesiveness & compressibility) themselvesact to enhance porosity and provide these pathways into the tablet. Liquid is drawn up or “wicked”into these pathways through capillary action and rupture the interparticulate bonds causing thetablet to break apart.. (Anon, 2016)

B. Swelling:

Although not all effective disintegrants swell in contact with water, swelling is believedto be a mechanism in which certain disintegrating agents (such as starch) impart the disintegratingeffect. By swelling in contact with water, the adhesiveness of other ingredients in a tablet isovercome causing the tablet to fall apart.. (Anon, 2016)

C. Because of heat of wetting (air expansion)

When disintegrants with exothermic properties gets wetted, localized stress is generateddue to capillary air expansion, which helps in disintegration of tablet. This explanation, however,is limited to only a few types of disintegrants and cannot describe the action of most moderndisintegrating agents.. (Anon, 2016)

D. Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegration attempts to explain the swelling of tablet made withnon-swell able disintegrants. Guyot-Hermann has proposed a particle repulsion theory based onthe observation that non-swelling particle also cause disintegration of tablets. The electricrepulsive forces between particles are the mechanism of disintegration and water is required for it.Researchers found that repulsion is secondary to wicking.. (Anon, 2016)

E. Due to deformation

Hess had proved that during tablet compression, disintegrated particles get deformed andthese deformed particles get into their normal structure when they come in contact with aqueousmedia or water. Occasionally, the swelling capacity of starch was improved when granules wereextensively deformed during compression. This increase in size of the deformed particles producesa breakup of the tablet. This may be a mechanism of starch and has only recently begun to bestudied. Starch grains are generally thought to be “elastic” in nature meaning that grains that aredeformed under pressure will return to their original shape when that pressure is removed. But,with the compression forces involved in tableting, these grains are believed to be deformed morepermanently and are said to be “energy rich” with this energy being released upon exposure towater. In other words, the ability for starch to swell is higher in “energy rich” starch grains than itis for starch grains that have not been deformed under pressure.. (Anon, 2016)

F. Due to release of gases

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressurewithin the tablet. This effervescent mixture is used when pharmacist needs to formulate veryrapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required duringmanufacturing of the tablets. The effervescent blend is either added immediately prior tocompression or can be added in to two separate fraction of formulation.. (Anon, 2016)

G. By enzymatic reaction

Here, enzymes presents in the body act as disintegrants. These enzymes destroy thebinding action of binder and helps in disintegration. It is believed that no single mechanism isresponsible for the action of most disintegrants. But rather, it is more likely the result of interrelationships between these major mechanisms. The classical example of the earliest knowndisintegrant is Starch. Corn Starch or Potato Starch was recognized as being the ingredient intablet formulations responsible for disintegration as early as 1906 (even though tabletdisintegration was itself not given much importance in tablet formulations until much later). Untilfairly recently, starch was the only excipient used as a disintegrant. To be effective, corn starchhas to be used in

concentrations of between 5-10%. Below 5%, there is insufficient “channels”available for wicking (and subsequent swelling) to take place. Above 10%, the incompressibilityof starch makes it difficult to compress tablets of sufficient hardness. Although the connection between bioavailability of drug and tablet disintegration took some time to become appreciated, it is now accepted that the role of the disintegrant is extremely important.. (Anon, 2016)

Other factors which affect the dissolution of Drugs from tablets are:

- Type and Concentration of Active Ingredient
- Type and Concentration of Binder Used
- Type and Concentration of Fillers Used (soluble vs. insoluble)
- Type and Concentration of Lubricant Used
- Type of Dissolution testing Used (Apparatus, Speed, Media)
- Manufacturing Process (wet granulation vs. compaction vs. direct compression)

In a direct compression process, drug is blended with a variety of excipients, subsequently lubricated and directly compressed into a tablet. A disintegrant used in this type of formulation, simply has to break the tablet apart to expose the drug substance for dissolution. In a wet granulation process, the drug substance is combined with other excipients and processed with the use of a solvent (aqueous or organic) with subsequent drying and milling to produce granules. The resulting granules are then blended with additional excipients prior to being compressed into a tablet. A disintegrant used in granulated formulation processes can be more effective if used both “intragranularly” and “extra granularly” thereby acting to break the tablet up into granules and having the granules further disintegrate to release the drug substance into solution. However, the portion of disintegrant added intragranularly (in wet granulation processes) is usually not as effective as that added extra granularly due to the fact that it is exposed to wetting and drying (as part of the granulation process) which reduces the activity of the disintegrant. Since a compaction process does not involve its exposure to wetting and drying, the disintegrant used intragranularly tends to retain good disintegration activity.. (Anon, 2016)

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1.4.5 Factors affecting action of disintegrants: Percentage of disintegrants present in the tablets.

- Types of substances present in the tablets.
- Combination of disintegrants.
- Presence of surfactants.
- Hardness of the tablets.
- Nature of Drug substances.
- Mixing and Screening. (Anon, 2016)

1.4.6. Effect of fillers:

The solubility and compression characteristics of fillers affect both rate and mechanism of disintegration of tablet. If soluble fillers are used then it may cause increase in viscosity of thepenetrating fluid which tends to reduce effectiveness of strongly swelling disintegrating agentsand as they are water soluble, they are likely to dissolve rather than disintegrate. Insoluble diluentsproduce rapid disintegration with adequate amount of disintegrants. Chebli and cartilier provedthat tablets made with spray dried lactose (water soluble filler) disintegrate more slowly due to itsamorphous character and has no solid planes on which the disintegrating forces can be exertedthan the tablet made with crystalline lactose monohydrate.. (Anon, 2016)

1.4.7. Effect of binder

As binding capacity of the binder increases, disintegrating time of tablet increases andthis counteract the rapid disintegration. Even the concentration of the binder can also affect thedisintegration time of tablet. . (Anon, 2016)

1.4.8 Effect of lubricants

Mostly lubricants are hydrophobic and they are usually used in smaller size than anyother ingredient in the tablet formulation. When the mixture is mixed, lubricant particles mayadhere to the surface of the other particles. This hydrophobic coating inhibits the wetting andconsequently tablet disintegration. Lubricant has a strong negative effect on the water uptake iftablet contains no disintegrants or even high concentration of slightly swelling disintegrants. Onthe contrary, the disintegration time is hardly affected if there is some strongly swellingdisintegrants are present

in the tablet. But there is one exception like sodium starch glycolatewhose effect remains unaffected in the presence of hydrophobic lubricant unlike otherdisintegrants. (Gohel, 2015)

1.4.9 Effect of surfactants

Sodium lauryl sulphate increased absorption of water by starch or had a variableeffect on water penetration in tablets. Surfactants are only effective within certain concentrationranges. Surfactants are recommended to decrease the hydrophobicity of the drugs because themore hydrophobic the tablet the greater the disintegration time. Aoki and fukuda claimed thatdisintegration time of granules of water-soluble drugs did not seem to be greatly improved by theaddition of nonionic surfactant during granulation , but the desired effect of a surfactant appearedwhen granule were made of slightly soluble drugs. The speed of water penetration was increasedby the addition of a surfactant.(Gohel, 2015)

1.5 Disintregrants used in tablets:

1.5.1 Starch

Starch is the oldest and probably the most widely used disintegrant in the pharmaceuticalindustry. Regular cornstarch USP, has certain limitation and has been replaced to some extent bymodified starches with specialized characteristics to serve specific functions. The mode of actionof starch is that the disintegrant forms pathways throughout the tablet matrix that enable water todraw into the structure by capillary action, thus leading to disruption of tablet. Other conceptrelates to swelling of starch grains on exposure to water, a phenomenon that physically rupturesthe particle – particle bonding in tablet matrix.(Anon, 2016)

1.5.2. Sodium starch glycolate

These are modified starches with dramatic disintegrating properties and are available asexplotab and primogel which are low substituted carboxy methyl starches. Explotab consists ofgranules that absorb water rapidly and swell. The mechanism by which this action takes placeresult in involves rapid absorption of water leading to an enormous increase in volume of granulesrapid and uniform disintegration. The natural pre-dried starches swell in water to the extent of 10-20 percent and the modified starches increase in volume by 200-300 percent in water. Thismodified starch is that the disintegration time may be independent of compression force,The tablets

formulated by using these disintegrants were disintegrated within twominutes. The higher dissolution rates observed with super-disintegrants may be due to rapiddisintegration and fine dispersion of particles formed after disintegration.(Anon, 2016)

Table 1.3:List of disintegrating agents:(Anon, 2016)

S.No	Disintegrants	Concentratin in granules%	S[ecial comments
1	Starch usp	5-20	Higher amount is required,poorlycompressable
2	Methylecellulose,NaCMc	5-10	-
3	Mycro crystalline cellulose	10-20	Lubricant properties and directly compressable
4	Na alginate	2.5 -10	Acts by swelling

1.5.3. Cross-linked polyvinyl pyrrolidone (cross povidone)

Kornblurn et al has reported the cross linked polyvinyl pyrrolidone and evaluated as tablet disintegrants and compared to starch USP and alginic acid. The capillary activity of cross povidone for water is responsible for its tablet disintegration property. Cross linked PVP has maximum moisture absorption and hydration capacity and can be considered for the selection of new disintegrant. They possess apparent binding property resulting in low percent of tablet friability, where it is employed as disintegrant even in low concentration 0.5 to 5 percent. Alesandro et al., 2001 formulated fast dissolving composition of ibuprofen tablet by using 0.5 to 10 % linear polyvinyl pyrrolidone with respect to ibuprofen. The tablet was completely in solution in 10 minutes.(Brook, 2015)

1.5.4. Cellulose

Cellulose such as purified cellulose, methylcellulose, cross-linked sodium carboxymethylcellulose (Ac-Di-Sol) and carboxy methyl cellulose are disintegrants to some extentdepending on their ability to swell on contact with water. A cross-linked form of Ac-Di-Sol hasbeen accepted as tablet disintegrant and it is essentially water insoluble. It has high affinity forwater, which results in rapid tablet disintegration.. (Celluloseether.com, 2013)

1.5.5. Microcrystalline cellulose

Microcrystalline cellulose exhibits good disintegrant property at low as 10 percent concentration. It functions by allowing water to enter the tablet matrix by means of capillary pores, which break the hydrogen bonding between adjacent bundles of cellulose microcrystals. Tablets with excess microcrystalline cellulose have a tendency to stick to the tongue due to rapid capillary absorption and dehydrating the most surface. Microcrystalline cellulose has a fast wicking rate for water, hence this and starch makes an excellent combination for effective and rapid disintegration in tablet formulation. To develop a rapidly disintegrating tablet, a mixture of MCC and L-HPC was in the range of 8:2 – 9:1 shown shortest disintegration time. MCC was used as disintegrating agent in the formulation of fast releasing compressed propranol hydrochloride suppositories as reported by Malladi et al. The concentration of MCC Shows faster drug release from suppository and evaluated their pharmacokinetics and pharmacodynamics performance and compared the result obtained with oral administration.. (Celluloseether.com, 2013)

1.5.6. Gums

Gums have been used as disintegrants because of their tendency to swell in water. They can display good binding characteristics (1 to 10 percent of tablet weight). This property can oppose the desired property of assisting disintegration and the amount of gum must be carefully titrated to determine the optimum level for the tablet. Common gums used as disintegrant include agar, locust bean, karaya, Pectin and tragacanth.(Carterpharmaceuticalconsulting.com, 2016)

Determination of flow property of amlodipine and propranolol against different ratio of CMC

1.5.7. Guar gums

It is naturally occurring gum (marketed under the trade name jaguar). It is free flowing, completely soluble, neutral polymer composed of sugar units and is approved for use in food. It is not sensitive to pH, moisture contents or solubility of the tablet matrix. It is not always pure white and sometimes varies in color from off-white to tan tends to discolor with time in alkaline tablets. It is used as disintegrants in the range of 0.5-5% showed rapid rate disintegration due to swelling of the gum.(Carterpharmaceuticalconsulting.com, 2016)

1.5.8. Gum Karaya

Karaya has the natural gum exudates from the traces of Sterculiaurens belonging to family sterculiacea. The high viscosity nature of gum limits its uses as binder and disintegrant inthe development of conventional dosage form.(Carterpharmaceuticalconsulting.com, 2016)

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1.5.9. Gellan gum

Gellan gum is a linear anionic polysaccharide, biodegradable polymer obtained from Pseudomonos elodea consisting of a linear tetra-saccharide repeat structure and use as a food additive. Antony et al studied the Gellan gum as a disintegrant and the efficiency of gum was compared with other conventional disintegrants such as dried corn starch, explotab, Microcrystalline cellulose (pH 102), Ac-di-sol and Kollidon CL. The disintegration of tablet might be due to the instantaneous swelling characteristics of gellan gum when it comes into contact with water and owing to its high hydrophilic nature. The complete disintegration of tablet was observed within 4 minutes with gellan gum concentration of 4 percent w/w and 90 percent of drug dissolved within 23 minute.(Carterpharmaceuticalconsulting.com, 2016)

1.5.10. Isapghula husk

It is a natural substance as disintegrant. It consists of dried seeds of the plant known as plantago ovata. It contains mucilage which is present in the epidermis of the seeds. The mucilage is used as binding agent in the granulation of material for compressed tablets. Plantago ovate seeds husk has high swellability and gives uniform and slightly viscous solution hence it is used as thickening and suspending agent. guptag.d. et al has investigated the disintegrating property of

the isapghula husk, cassia tora and cassia nodosa and the formulations were evaluated for the standard of dispersible tablets and were compared with marketed products. the study shown that the natural gums used as disintegrants were effective in low (5%) concentrations.(Carterpharmaceuticalconsulting.com, 2016)

1.5.11. Polacrillin potassium (tulsion)

Tulsion (339) is a resin consisting of highly purified cross-linked polacrillin copolymer in potassium form. It is used as a tablet disintegrant and as a taste-masking agent for various drugs. When tulsion-339 is used as disintegrant, it swells up at very fast rate upon contact with water or gastro intestinal fluid and act as an effective tablet disintegrant. It is to be added in a dry form in the proportion of 0. 5 to 5% of the total weight of tablet, amount may vary depending upon nature of tablet. polacrillin potassium is high molecular weight polymer so can't be absorbed by body tissues & is safe for human consumption. It has no any physiological action at recommended dosage & it is non-toxic.

Specific features of tulsion-339 as a disintegrant:

-Faster rate of swelling.

-No lump formation after disintegration / dispersion.

- High compatibility. With excipitients and common therapeutic agent.

-Does not stick to punches and clays.(Carterpharmaceuticalconsulting.com, 2016)

1.5.12. Agar

Agar is the dried gelatinous substance obtained from GelidiumAmansii(Gelidanceae) and several other species of red algae like, Gracilaria (Gracilariaceae) and Pterocadia (Gelidaceae). Agar is yellowish gray or white to nearly colorless, odorless with mucilaginous taste and is available in the form of strips, sheet flakes or coarse powder. Agar consists of two polysaccharides as agarose and agaropectin. Agarose is responsible for gel strength and Agaropectin is responsible for the viscosity of agar solutions. High gel strength of agar makes it a potential candidate as a disintegrant. Ito et al investigated the use of agar powder as a disintegrating agent for the development of rapidly disintegrating oral tablets. Agar was chosen

because it absorbs water and swells significantly but do not become gelatinous in water at physiological temperature.(Carterpharmaceuticalconsulting.com, 2016)

1.5.13. Gas – evolving disintegrants

Another approach for the disintegration of tablet is inclusion of citric acid and tartaric acid along with the sodium bicarbonate, sodium carbonate, potassium bicarbonate or calcium carbonate. These react in contact with water to liberate carbon dioxide that disrupts the tablet. Onali et al described the process of making rapidly disintegrating tablets. The tablets consisting of malic acid or effervescence base, calcium carbonate as an active ingredient (antacid) and cornstarch as a bulking agent and disintegrating agent. The tablets prepared from these ingredients disintegrated within 20 second.(Carterpharmaceuticalconsulting.com, 2016)

1.6 ADVANTAGES:

- Effective in lower concentrations than starch

-Less effect on compressibility and flow ability

-More effective intragranularly.(Carterpharmaceuticalconsulting.com, 2016)

1.7 DISADVANTAGES:

-More hygroscopic (may be a problem with moisture sensitive drugs)

-Some are anionic and may cause some slight in-vitro binding with cationic drugs (not a problem in-vivo.)(Carterpharmaceuticalconsulting.com, 2016)

1.8 Carboxy Methyl Cellulose

1.8.1 Appearance and Solubility

The pure Sodium Carboxy methyl Cellulose is white or milk white fibrous powder or particles, odorless and tasteless. It is insoluble in organic solvents such as methanol, alcohol, diethyl ether, acetone, chloroform and benzene but soluble in water. Degree of substitution is an important factor influencing water solubility and the viscosity of Sodium carboxy methylcellulose also has a great effect on the water solubility.

In general when the viscosity is within 25-50Pa•s and the degree of substitution is about 0.3, it shows alkaline solubility and while the degree of substitution is over 0.4, it shows water solubility. With the rise of DS, the transparency of solution improves accordingly. In addition, the replacement homogeneity also has an great effect on the solubility.(Celluloseether.com, 2013)

1.8.2 Hygroscopicity

Sodium carboxy methylcellulose equilibrium water content will increase with the rise of air humidity but decrease with the rise of temperature. At room temperature and average humidity of 80-85%, the equilibrium water content is more than 26% but moisture content in the products is lower than 10%, lower than the former. As far as its shape is concerned, even if the water content is about 15%, there seems no difference in appearance.(Celluloseether.com, 2013)

However, when the moisture content reaches above 20%, inter-particle mutual adhesion can be perceived and the higher the viscosity is, the more evident it will become. For these polarized high-molecular compounds like Sodium carboxy methylcellulose, the hygroscopic degree is not only affected by the relative humidity but also by the number of polarity. The higher the degree os substitution is, that is, the larger the number of polarity, the stronger the hygroscopicity will be. Moreover, crystallinity also affects it and the higher the crystallinity is, the smaller the hygroscopic will be.(Celluloseether.com, 2013)

1.8.3 Compatibility

Sodium carboxy methylcellulose has good compatibility with other kinds of water-soluble glues, softeners and resin. For example, it is compatible with animal glues, dimethoxy dimethylurea gel, Arabic gum, pectin, tragacanth gum, ethylene glycol, sorbitol, glycerol, invert sugar, soluble starch and sodium alginate. It is also compatible with casein, the compound of melamine-formaldehyde resin and ethylene glycol, urea formaldehyde ethylene glycol resin, methyl cellulose, polyvinyl alcohol (PVA), phosphate nitrilotriacetic acid, and sodium silicate but the degree is slightly poorer. 1% Sodium carboxy methylcellulose solution is compatible with most inorganic salts.(Celluloseether.com, 2013)

1.8.4 Dissociation Constant

In the giant polymer matrix of Sodium carboxy methylcellulose, there are plenty of electrolyzing groups (carboxy methyl groups). The acidity is similar to that of acetic acid and the dissociation constant is 5×10-5. The dissociation strength has a considerable effect on the electrical properties of Sodium carboxy methylcellulose.(Celluloseether.com, 2013)

1.8.5 Biochemical Properties

Although Sodium carboxy methylcellulose solution is difficult to get rotten than natural gums, under certain conditions, some microbes enable it to get rotten, especially with cellulose and taka-amylase reactions, leading to the decrease of solution viscosity. The higher the DS of Sodium carboxy methylcellulose is, the less it will be affected by enzymes and this is because the side chain linked with glucose residues prevents enzymolysis.(Celluloseether.com, 2013)

Since the enzyme action leads to the breakage of Sodium Carboxy methyl Cellulose main chain and generates reducing sugar, in this way the degree of polymerization will decrease and the solution viscosity will accordingly decrease. The digestive enzymes within human body can have no decomposition on Sodium carboxy methylcellulose and Sodium carboxy methylcellulose has no decomposition in acid or alkaline digestive juice.(Celluloseether.com, 2013)

1.9 Short Notes on other excipients used in this experiment

1.9.1 Calcium phosphate: It was used as diluent. Unlike most other compounds, the solubility level of calcium phosphate becomes lower as temperature increases. Thus heating causes precipitation.(Wikiwand, 2016)

1.9.2 Lactose: It was also used as diluent. Lactose (milk sugar) is a disaccharide that consists of glucose and galactose.(Www3.hhu.de, 2016)

1.9.3 Starch: It was used as diluent. Starches are carbohydrates in which 300 to 1000 glucose units join together. It is a polysaccharide.(Hyperphysics.phy-astr.gsu.edu, 2016)

1.9.4 Polyethylene glycol: It was used as binder. Polyethylene glycol (PEG) is a condensation polymer of ethylene oxide and water.(Brook, 2015)

1.9.5 Polyvinyl pyrrolidone: It was used as binder. It is also commonly called polyvidone or povidone, is a water-soluble polymer made from the monomer N-vinylpyrrolidone.(Brook, 2015)

1.9.6 Magnesium Stearate: It was used anti adherent**.** Magnesium stearate is produced by the reaction of sodium stearate (a salt of stearic acid chiefly found in the manufacture of soap) with magnesium sulfate, better known as Epsom salt.(Scout and Scout, 2015)

1.9.7 Zinc stearate: It was also used as anti-adherent. (Scout and Scout, 2015)

1.9.8 Talc: It was used as lubricant. It is very soft mineral.(Gohel,2015)

1.9.9 Sodium Lauryl sulphate: It was used as lubricant.(Fioravanti, 2010)

Chapter 2:

Literature Review

2.1 Literature Review

Around 80% of drug dosage forms is covered by solid dosage forms, like tablet, capsules etc. Powder flow characteristic is one of the most important parameter to be checked in case of these dosage preparations. Flow ability of the formulations for the dosage forms, including both active pharmaceutical ingredients and powder excipients, is usually tested while the ingredients flow by the research team. After their approval for certain ingredients, flow property is further tested commercially by the team within a pharmaceutical to be assured of whether this formulation is appropriate for bulk scale preparation or not. This flow characteristic determination of pharmaceutical ingredients has been continuing for many decades, and the researcher finally reached to a conclusion about using any ingredient, or benefits or problems of few ingredients together. Some of the studies are overviewed in the following of this review.

In the year 1965 Gold and Palermo described the instrumentation for measuring the sign and magnitude of static charges produced by particles flowing through a tablet hopper. They took acetaminophen in crystalline form, which had a higher negative hopper flow static charge than granulation prepared from the powder. At the end of the study, they concluded that other tablet excipient, such as diluents (egdicalcium phosphate dihydrate, mannitol, spray-dried lactose) and lubricants like magnesium stearate and talc declined the hopper flow static charge of active drug, acetaminophen. They also showed that particle size and water concentration influence the magnitude of the hopper flow static charge.

In the last of the following year, again Gold, with his another research team studied the effect of different parameters of glidants on its flow rate and angle of repose. Glidants is often selected by subjective methods like measurement of the angle of repose. They compared the both results; one is by using the glidants practically in tablet preparation and thus checking its flowability, and other result was achieved by identifying their angle of repose. They took some widely used glidants for their study, like fumed silicon dioxide, starch, magnesium stearate, and talc, in combination with selected materials. Many of the more commonly used glidants actually decreased the flow rate. Glidants, which lowered the angle of repose of the tablet formula did not necessarily enhance the flow rate and noticeable changes in flow rate were not always visible by angle of repose measurement. Finally they concluded the study by showing that, a comparison between the angle of repose of a particular glidant and the flow rate of it using with various

common raw materials indicated that the angle of repose was not a consistent method for assessing the flow of these materials. (Gold, et al., 1966)

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)

In the year 1982, a study was performed showing the effect of particle size on the compression mechanism and tensile strength of prepared tablets. 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 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 after many more years Kamath, Puri and Manbeck measured the flow properties such as cohesion and slope of the yield of wheat flour at various moisture contents by using the Jenike

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

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

In following year Amidon with Houghton (1995) showed the effect of moisture on the mechanical and powder flow properties of microcrystalline cellulose (MCC). Mechanical properties of MCC were determined on different range of moisture (0 to 12.2%) and few other parameters were also checked, such as, compaction, hardness study, compressibility index and also shear cell index. They found significant changes in the results as the moisture level of the excipient was increasing. The permanent deformation pressure and tensile strength of compacts were monitored to be relatively independent of moisture content below about 5% moisture and then decrease as the moisture content increased further. Above 5% of moisture level the flow rates of MCC were getting poorer as the moisture level increased, and it was identified by the value achieved from Compressibility index and using shear cell method. The data of mechanical property are consistent with the hypothesis they made that water acts as a plasticizer and influences the mechanical properties of microcrystalline cellulose. At moisture levels above about 5%, the material exhibits significant changes consistent with a transition from the glassy state to the rubbery state. (Amidon with Houghton, 1995)

In 1996, Rajesh Patel and FridrunPodczeck investigated 8 microcrystalline cellulose samples on the capsule filling performance. Different sources of fine, medium and coarse grade microcrystalline cellulose were used. They determined the Kawakita constant and Hausner's ratio

as the indicators of the capsule filling performance. A fine grade microcrystalline cellulose such as Avicel® PH105 cannot be used in capsule filling because of unsatisfactory flow properties. 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 the same year a comparative investigation has been performed by Talukdar and other scientists between xanthan gum and HPMC which act as hydrophilic matrix-forming agents. They observed the compaction characteristics and drug release behavior of these materials. Though the compaction characteristics were found similar but the flow characteristics were different. HPMC is less flowable than xanthan gum which significantly affects the drug release profiles of these potential excipients.(Talukdar et al., 1996)

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

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).

In the year 2001, Gabaude and his research team studied on four characterisation techniques, such as packing and rearrangement under pressure methods or shear cell measurement methods, used to assess powder flow properties. They used mercury porosimetry and two compressibility methods and analyzed the reduction of the powder bed volume under low pressures. They determined flow functions, deduced from shear cell measurements using a JohansonIndicizer Tester. Their examination of the reduction of the powder bed volume leads to new parameters

such as the packing coefficient and the volume of mercury interrupted. They found that packing coefficient appears to be a reliable approximation of powder flow properties. They found that it is actually well correlated with shear cell measurements and it is more accurate than classical flowability tests recommended by the European Pharmacopoeia. Finally they concluded that this method is able to give very early in the development, a quite accurate estimation of powder flow properties of new drug substances and this may be very helpful for an early determination of the optimum particle granulometry or for a rapid development of a feasible industrial process. (Gabaude, et al., 2001)

In the March of 2002, an Indian scientist, Vijay Kumar along with two others conducted a study with UICEL that is actually a new cellulose-based tabletting excipient. This has been developed by treating cellulose powder with an aqueous solution of NaOH (conc. ≥5N) and subsequently precipitating it with ethyl alcohol. UICEL is similar in structure to Avicel® PH-102, a commercial direct compression excipient commonly referred to as microcrystalline cellulose (MCC). Compared to Avicel® PH-102, UICEL shows higher true density, bulk density, tap density, Carr's index and Hausner ratio values. The mean deformation pressure (Py) values calculated from the linear portion of the Heckel plots for UICEL and Avicel® PH-102 were about 104 and 87 MPa, respectively, suggesting that UICEL is less pliable than Avicel® PH-102. The hardness values of UICEL tablets increased nearly linearly with increasing compression pressures. Avicel® PH-102 formed stronger tablets in comparison to that made up of UICEL. Irrespective of the compression pressure used, all UICEL tablets disintegrated within 15 s, whereas Avicel® PH-102 tablets of comparable strengths remained intact for over 12 h. The whole study concluded that UICEL can be used as a direct compression excipient, especially in the design and development of fast-disintegrating tablets. (Kumar, Reus-Medina, Yang, 2002)

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

Again at the end of that year, Zhang and his fellow researchers came out with another analysis. They investigated the basic physico-chemical property and binding functionality of commonly used commercial direct compression binders/fillers through their study. The compressibility of these materials was also analyzed using compression parameters derived from various sources, like Heckel, Kawakita, and Cooper-Eaton equations. They evaluated five classes of excipients, including microcrystalline cellulose (MCC), starch, lactose, dicalcium phosphate (DCP), and sugar. In general, the starch category exhibited the highest moisture content followed by MCC, DCP, lactose, and finally sugars; DCP displayed the highest density, followed by sugar, lactose, starch, and MCC; the material particle size is highly processing dependent. The data also exhibited that MCC had moderate flowability, excellent compressibility, and extremely good compact hardness; with some exceptions among starch, lactose, and sugar. This research additionally confirmed the binding mechanism that had been well documented: MCC performs as binder because of its plastic deformation under pressure; fragmentation is the predominant mechanism in the case of lactose and DCP; starch and sugar perform by both mechanisms. (Zhang, Law, Chakrabarti, 2003)

In the next year 2004, Bhattachar and his research fellows studied on the flow properties of pharmaceutical powders and blends used in solid oral dosage forms which are important consideration during dosage form development. They adapted vibratory feeder method which is a flow measurement technique that quantifies avalanche flow that used for measurement of the flow properties of common pharmaceutical powders used in solid oral dosage forms. They measured 17 different powders with the instrument and results are described as a powder flow index (PFI). They found the PFI tendency of the powders show a relationship with flow properties. They also measured the flow property with a commercially available avalanche instrument, the Aero-Flow™, and the results were detailed as the mean time to avalanche (MTA). in view of the fact that the two instruments analyze the avalanche by different algorithms, the results were compared with nonparametric statistical evaluation of ranked data. Finally they recommended a procedure for measurement of powder flow with the vibratory feeder. (Bhattachar, 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)

In the same year, an experiment was done to determine the effect of powder properties and its storage condition on the flowability of milk powders with different fat contents. Consistent reliable flow of milk powders out of hoppers is very important in their handling and processing. Shear cell methods were applied in this work to measure and compare the flow characteristics of a commercial skim-milk powder (SMP), a whole milk powder (WMP) and a 73% high fat milk powder (HFP), and to examine how storage temperature and exposure to moisture in air affected

the flowability of these milk powders. This technique was also used to investigate how powder particle size and free-fat content affected the flowability of a number of milk powders produced at pilot-scale. WMP and HFP were cohesive powders while SMP was easy flow, but SMP showed greater wall friction on the stainless steel material tested. Decreasing particle size from 240 to 59 μm produced a major increase in cohesion of 26% fat milk powders. (Fitzpatrick, 2004)

Again in the year 2004, a pioneer research team introduced the world a statement that in the development of dosage form, the flow properties of pharmaceutical excipients in solid oral dosage forms is a fundamental phenomenon. In this case, the vibratory feeder method was considered as the flow measurement technique to measure flow properties of common excipients in solid oral dosage forms. In this experiment, seventeen different powders were evaluated with the instrument to measure the flow properties and the result was stated as the powder flow index (PFI). On the other hand, the powder flow was evaluated with another commonly used avalanche instrument and similarly the data was included in mean time to avalanche (MTA) as mean time. The results obtained from the two different instrumental methods (PFI and MTA) having different algorithms, were compared with nonparametric statistical assessment of the data and proved as a reliable document. Afterwards, vibratory feeder method was recommended for measuring powder flow. (Bhattachar, 2004)

In 2005, Jun Yang and Ales Sliva indicated that surface-treated hydrophobic silica ismore effective in improving the flowability of cornstarch particles than untreatedhydrophilic silica (Yang, 2005).

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

In the year 2007, another study was conducted on flow property of co-processed particles of microcrystalline cellulose (MCC) and mannitol. Both the excipients were fabricated by spray drying process to be used as a direct compression excipient in fast dissolving tablet formulation. The composite particles were examined for their powder and compression properties. The scientists observed that an increase in the MCC proportion imparted greater compressibility to

the composite particles, but the flowability of these mixtures was decreased. Although MCC and mannitol have been widely used in the formulation of fast dissolving tablets, the non-wetting property of the hard compact central core may delay the disintegration time. Optimizing the ratio of mannitol and MCC in 1.25:1, the scientists found to have optimized powder and compressibility characteristics with fast disintegrating property (<15 s). It was concluded that a higher rate of powder flow can indirectly influence the rate of disintegration. (Jacob, 2007)

In 2008, Hou and Sun investigated the effects of particle size, morphology, particle density, and surface silicification, on powder flow properties using a ring shear tester. They took 11 powders from three series of microcrystalline cellulose (MCC) (a) Avicel, regular MCC, elongated particles, (b)Prosolv, silicified MCC, elongated particles, and (c) Celphere, spherical MCC, and studied them. They found that smaller particles always led to poorer powder flow properties. They identify that mechanism of the detrimental effect of particle size reduction on flow properties and that was the larger powder specific surface area. They found that flow properties of Celphere were considerably better than Avicel of comparable particles size and finally suggested that spherical morphology promoted better powder flow properties. They identified that flow properties of powders different in densities but similar in particle size, shape, as well as theyfound similar surface properties.(Hou and Sun ,2008)

Rakhi B. Shah, Mobin A. Tawakkul, and Mansoor A. Khancorresponding in 2008 worked to investigate the systematic evaluation of flow of pharmaceutical powders and granules using compendial and non-compendial methods. Angle of repose, bulk density, tapped density, Carr's compressibility index, and Hausner ratios were evaluated. Additionally, flow was characterized using a powder rheometer in which a sensitive force transducer monitors the forces generated as a result of the sample displacement. The critical attributes such as cohesivity index, caking strength, and flow stability were determined for samples. The samples consisted of different grades of magnesium stearate powder including bovine, vegetable, and food grade, physical mixture powder blend consisting of a model formulation, granules prepared by various methods including slugging, high shear granulator, and fluid bed dryer. Lubricant efficiency was also determined for granules lubricated with various concentrations of magnesium stearate. It was observed that the compendialmethods were often non-discriminating for minor variations in powder flow. The additional characterization such as cohesivity, and caking strength were

helpful in understanding the flow characteristics of pharmaceutical systems. The flow stability test determined that the powders were not affected by the test conditions on the rheometer. The non-compendial tests were discriminating to even minor variations in powder flow.(Mobin A, Mansoor A. Khancorresponding and Rakhi B. Shah,2008)

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

Sarraguca and his fellow researchers studied the flow properties of pharmaceutical excipientss using near infrared spectroscopy. They illustrated that physical properties of pharmaceutical powders are of topmost significance in the pharmaceutical industry. They examined the critical significant properties of flowability using processes like blending, tablet compression, capsule filling and transportation using angle of repose, Carr's index and Hausner ratio. They used near infrared spectroscopy because it is fast and low-cost analytical technique to determine the parameters of flow properties of pharmaceutical powders based on active ingredient paracetamol. The spectra were recorded on a Fourier-transform near infrared spectrometer in which the parameters were the angle of repose, true and tapped density. The comparison was made between near infrared based properties and reference methods results. The result showed that the physical properties affect the flowability of pharmaceutical powders. The correlation between the reference method values and the near infrared spectrum was carried out and both the results were compared. They concluded the study showing that prediction errors varied between 2.51% for the tapped density, 3.18% for the bulk density and 2.35% for the angle of repose. (Sarraguca ,2010)

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In 2013 MileneMinniti de Campos and Maria do CarmoFerreira measured and compared the flow properties of two alumina-based powders. The alumina powder (AP) is irregularly shaped and has a smooth surface and moisture content of 0.16%, and the ceramic powder (CP), obtained after atomization in a spray dryer, is spherical and has a rough surface and moisture content of 1.07%. We measured the Hausner ratio (HR), the static angle of repose (AoR), the flow index (FI), the angle of internal friction, and the wall's friction angle. The properties measured using aerated techniques (AoR and HR) demonstrated that AP presents true cohesiveness (and therefore a difficult flow), while CP presents some cohesiveness and its flow might be classified as half way between difficult and easy flow. Their FI values, which were obtained using a nonaerated technique, enable us to classify the alumina as cohesive and the ceramic powder as an easy-flow powder. The large mean diameter and morphological characteristics of CP reduce interparticle forces and improve flowability, in spite of the higher moisture content of their granules. The angles of internal friction and of wall friction were not significantly different when comparing the two powders. (MileneMinniti de Campos and Maria do CarmoFerreira, 2013)

Chapter 3:

Materials and Methods

Determination of flow property of amlodipine and propranolol against different ratio of CMC

3.1 MATERIALS

3.1.1 Excipients Collection:

For the research purpose different classes of excipients were collected from the different labs of Pharmacy Dept. of East West University**.**

3.1.2 Excipients:

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

Table-3.1 : List of excipients through this research work.

SL no.	**Name of Excipients**	**Source (Supplier Name)**
1.	Calcium Phosphate	MERK, Germany
2.	Polyvinyl Pyrrolidone	MERK, Germany
3.	CMC	MERK, Germany
4.	Zn Stearate	MERK, Germany
5.	Talc	MERK, Germany

3.2 Equipments and Instruments:

Table-3.2: List of instruments through this research work.

Serial No	Equipments	Source (Supplier Name)	Origin
1.	Weight Balance	SHIMADZU	Japan

Fig 3.1: Electronic Balance

Fig 3.2: Rough Balance

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3.2.1 Apparatus:

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

Table-3.3: List of apparatus used throughout this research work.

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

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3.3 METHODS

3.3.1 Preparation of various set of formulas:

Several number of same type formulas of a combination of excipients which includes lubricants, disintegrants, binders and antiadherents were made. In all set of formulas CMC ratio were varied in some set amlodipine or PropranololHCl was added. In the amlodipine containing sets all ratios contain same amount of amlodipine. In the Propranolol HCl containing sets all ratios contain same amount of Propranolol HCl. In these ways various formulas were made of 3g.

3.3.2 Flow property measurement

3.3.2.1 Determination of bulk volume:

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

3.3.2.2 Determination of tapped volume:

After measuring the bulk volume, the mixture of materials in the measuring cylinder was tapped manually 50 times and above until little further volume change is observed. The tapping is achieved by raising the cylinder and allowing it to drop under a specified distance. Themeasured volume was documented

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3.3.2.3 Calculation of Carr'sindex and Hausnerratio:

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

Compressibility Index=100× ($V_0 - V_f / V_0$)

Hausner Ratio= V_0/V_f

Where, Vo= Bulk volume

Vr = Tapped volume

3.3.2.4 Measurement of Angle of repose:

In this research project fixed funnel method was used.

3.3.2.4.1 Procedure:

First of all, funnel made of plastic, glass or stainless steel was set with the holding stand tightly. The funnel was fixed in a place, 4 cm above the bench surface. On the bench surface, a piece of paper was placed. The mixture of the running test tube was poured through the funnel without incorporating external pressure or stress. The powder mixture formed a cone on the paper. After the cone from 3g of sample was built, height of the granules forming the cone (h) in cm and the radius (r) of the base in cm were measured. The angle of repose was calculated by the given formula and documented.

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

Where, h = height of the powder cone from the base;

r = radius of the conical pile.

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3.3.3 Preparation of Formulas:

3.3.3.1 Preparation of Formula, F:

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

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

Ingredients Name	Purpose of Use	Percentage	Quantity(in g)
Calcium Phosphate	Lubricant	45%	4.5
PEG	Disintegrant	25%	2.5
Mg Stearate	Antiadherent	15%	1.5
Talc	Binder	15%	1.5
		Total:100%	Total:10g

3.3.4 Preparation of Different Sets:

3.3.4.1 Preparation of Set-1:

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

Determination of flow property of amlodipine and propranolol against different ratio of CMC

Table-3.5: The amount of CMC and F in different ratios (Set-1) in 3g.

Ratio	**CMC : F**	**Amount of CMC: F (in g)**
1	3% : 97%	0.09:2.91
2	5% : 95%	0.15:2.85
3	7% : 93%	0.21:2.79
4	9% : 91%	0.27:2.73
5	11% :89 %	0.33:2.67

3.3.4.2 Preparation of Set-2:

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

Table-3.6: The amount of CMC and F in different ratios (Set-2) in 3g.

Ratio	**CMC: F**	**Amount of CMC : F (in g)**
1	4% : 96%	0.12:2.88
2	8% : 82%	0.24:2.76
3	12% : 88%	0.36:2.64
4	16% : 84%	0.48:2.52
5	20% : 80%	0.6:2.4

Determination of flow property of amlodipine and propranolol against different ratio of CMC

3.3.4.3 Preparation of Set-3:

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

Table-3.7: The Amount of CMC and F in Different Ratios (Set-3) in 3g.

Ratio	**CMC : F**	**Amount of CMC: F (in g)**
1	6% : 94%	0.18:2.82
2	12% : 88%	0.36:2.64
3	18% : 82%	0.54:2.46
4	24% : 86%	0.72:2.28
5	30% : 70%	0.90:2.1

3.3.4.4 Preparation of Amlodipine Set-1:

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

Determination of flow property of amlodipine and propranolol against different ratio of CMC

Table-3.8: Amlodipine Containing Different Ratios (Amlodipine Set-1) in 3g.

Ratio	**CMC : F**	**Amount of CMC : F (in g)**	**Amlodipine added(in g)**
1	3% : 97%	0.09:2.91	0.0875
2	5% : 95%	0.15:2.85	0.0875
3	7% : 93%	0.21:2.79	0.0875
4	9% : 91%	0.27:2.73	0.0875
5	11% :89 %	0.33:2.67	0.0875

3.3.4.5 Preparation of Amlodipine Set-2:

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

Table-3.9: Amlodipine Containing Different Ratios (Amlodipine Set-2) in 3g.

Ratio	**CMC : F**	**Amount of CMC : F (in g)**	**Amlodipine added(in g)**
1	4% : 96%	0.12:2.88	0.0875
2	8% : 82%	0.24:2.76	0.0875
3	12% : 88%	0.36:2.64	0.0875
4	16% : 84%	0.48:2.52	0.0875
5	20% : 80%	0.6:2.4	0.0875

Determination of flow property of amlodipine and propranolol against different ratio of CMC

3.3.4.6 Preparation of Amlodipine Set-3:

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

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

Ratio	CMC : F	Amount of CMC: F (in g)	Amlodipine added(in g)
1	6% : 94%	0.18:2.82	0.0875
2	12% : 88%	0.36:2.64	0.0875
3	18% : 82%	0.54:2.46	0.0875
4	24% : 86%	0.72:2.28	0.0875
5	30% : 70%	0.90:2.1	0.0875

3.3.4.7 Preparation of Propranolol Set-1:

Propanolol HCl was added to remaining ratio of set-1. I had assume 80 mg of Propanolol HCl tablet contains 5mg of Propanolol HCl. 1.4 g or 1400 mg contain 87.5 mg or 0.0875 g of Propanolol HCl.

Table-3.11: Propranolol Containing Different Ratios (Propanolol Set-1) in 3g.

Ratio	CMC : F	Amount of CMC: F (in g)	Propanolol HCl added (in g)
1	3% : 97%	0.09:2.91	0.0875
2	5% : 95%	0.15:2.85	0.0875
3	7% : 93%	0.21:2.79	0.0875
4	9% : 91%	0.27:2.73	0.0875
5	11% :89 %	0.33:2.67	0.0875

Determination of flow property of amlodipine and propranolol against different ratio of CMC

3.3.4.8 Preparation of Propranolol Set-2:

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

Table-3.12: Propranolol Containing Different Ratios (Propanolol Set-2) in 3g.

Ratio	CMC: F	Amount of CMC : F (in g)	Propanolol HCl added (in g)
1	4% : 96%	0.12:2.88	0.0875
2	8% : 82%	0.24:2.76	0.0875
3	12% : 88%	0.36:2.64	0.0875
4	16% : 84%	0.48:2.52	0.0875
5	20% : 80%	0.6:2.4	0.0875

3.3.4.9 Preparation of Propranolol Set-3:

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

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

Ratio	CMC: F	Amount of CMC: F (in g)	Propanolol HCl added (in g)
1	6% : 94%	0.18:2.82	0.0875
2	12% : 88%	0.36:2.64	0.0875
3	18% : 82%	0.54:2.46	0.0875
4	24% : 86%	0.72:2.28	0.0875
5	30% : 70%	0.90:2.1	0.0875

Chapter 4:

Result

Determination of flow property of amlodipine and propranolol against different ratio of CMC

4.1: Results:

4.1.1 Calculation of individual excipients flow properties:

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

Determination of flow property of amlodipine and propranolol against different ratio of CMC

4.1.1.1 Result of the Ratios of the Set-1:

4.1.1.1.1 Carr's Index and Hausner's Ratio:

Ratio	Bulk Volume, Vo (ml)	Most Acceptable Value of Vo (ml)	Tapped Volume, Vr (ml)	Most Acceptable value of Vr	Hausner's Ratio	Compressibility index (%)
1 (3%: 97%)	7.2 7.1 7.0	7.0	5.90 5.80 5.90	5.80	1.21	17.14
2 (5%: 95%)	7.5 7.4 7.2	7.50	5.84 5.88 5.85	5.84	1.28	22.13
3 (7%: 93%)	7.5 7.7 7.8	7.80	5.90 5.89 5.90	5.89	1.32	24
4 (9%: 91%)	8 7.95 7.98	8	6 6.00 6.00	6.00	1.33	25
5 (11%: 89%)	8.40 8.50 8.55	8.55	6.50 6.20 6.45	6.20	1.37	27

Determination of flow property of amlodipine and propranolol against different ratio of CMC

Table-4.1: Carr's index and Hausner ratio measured for set-1.

4.1.1.1.2 Angle of Repose Measurement for the Ratios of Set-1:

Table-4.2: Angle of Repose Measured For The Ratios of Set-1.

Ratio	Height (h)	Average Height (h)	Diameter (2r)	Average Diameter (2r)	Radius (r)	Angle of Repose (o)
1 (3%: 97%)	1.9	1.73	4.6	4.8	2.4	35.79
	1.8		4.8			
	1.7		5			
2 (5%: 95%)	1.77	1.78	4.7	4.6	2.3	37.73
	1.78		4.5			
	1.79		4.6			
3 (7%: 93%)	1.9	1.80	4.1	4	2	41.99
	1.7		3.9			
	1.8		4			
4 (9%: 91%)	1.8	1.84	3.9	3.9	1.95	43.34
	1.88		3.8			
	1.85		4.0			
5 (11%: 89%)	1.9	1.89	4.0	3.87	1.93	44.40
	1.89		3.7			
	1.88		3.9			

Determination of flow property of amlodipine and propranolol against different ratio of CMC

4.1.1.2 Results of the Ratios of Set-2:

4.1.1.2.1 Carr's Index and Hausner's Ratio Measurement for the Ratios of Set-2:

Table-4.3:Carr's index and Hausner ratio measured for set-2.

Ratios	Bulk Volume, Vo (ml)	Most Acceptable Value of Vo (ml)	Tapped Volume, V_f(ml)	Most Acceptable value of V_f	Hausner's Ratio	Compressibility index (%)
1 (4%: 96%)	7.5 7.4 7.5	7.5	6 6.1 6.2	6	1.25	20
2 (8%: 92%)	7.8 7.7 7.7	7.8	6.1 6.2 6.1	6.1	1.27	21.79
3 (12%: 88%)	8 7.9 7.8	8	6.2 6.4 6.5	6.2	1.29	22.5
4 (16%: 84%)	8.4 8.2 8	8.4	6.4 6.6 6.4	6.4	1.31	23.81
5 (20%: 80%)	8.8 8.5 8.8	8.8	6.6 6.6 6.7	6.6	1.33	25

4.1.1.2.2 Angle of Repose Measurement forthe Ratios of Set-2:

Table-4.4: Angle of Repose Measured For The Ratios of Set-2.

Ratios	Height (h)	Average Height (h)	Diameter (2r)	Average Diameter (2r)	Radius (r)	Angle of Repose (o)
1 (4%: 96%)	1.8	1.79	4.7	4.63	2.31	37.77
	1.78		4.6			
	1.79		4.6			
2 (8%: 92%)	1.81	1.80	4.6	4.53	2.26	38.53
	1.8		4.5			
	1.79		4.5			
3 (12%: 88%)	1.85	1.83	4.5	4.33	2.17	40.14
	1.81		4.2			
	1.82		4.3			
4 (16%: 84%)	1.87	1.88	4.1	4.13	2.07	42.25
	1.88		4.2			
	1.88		4.1			
5 (20%: 80%)	1.9	1.90	4	4.03	2.02	43.25
	1.91		4			
	1.9		4.1			

4.1.1.3 Results of the Ratios of the Set-3:

4.1.1.3.1 Carr's Index and Hausner's Ratio Measurement for the Ratios of Set-3:

Table-4.5: Carr's index and Hausner ratio measured for set-3.

Ratio	Bulk Volume, Vo (ml)	Most Acceptable Value of Vo (ml)	Tapped Volume, V_f (ml)	Most Acceptable value of V_f	Hausner's Ratio	Compressibility index (%)
1 (6%: 94%)	7.7 7.6 7.5	7.7	6.3 6.2 6.3	6.2	1.24	19.5
2 (12%: 88%)	8.4 8.2 8.3	8.4	6.4 6.4 6.5	6.4	1.31	23.81
3 (18%: 82%)	8.7 8.8 8.8	8.8	6.4 6.7 6.7	6.4	1.38	27.27
4 (24%: 76%)	9.1 9.2 9.1	9.2	6.6 6.80 6.80	6.6	1.39	28.26
5 (30%: 70%)	9.6 9.4 9.5	9.5	6.80 6.80 7.00	6.8	1.41	29.17

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4.1.1.3.2 Angle of Repose Measurement forthe Ratios of Set-3:

Table-4.6: Angle of Repose Measured For The Ratios of Set-3.

Ratio	Height (h)	AVr Height (h)	Diameter (2r)	AVr Diameter (2r)	Radius (r)	Angle of Repose (o)
1 (6%: 94%)	1.8	1.80	4.7	4.6	2.3	38
	1.8		4.6			
	1.8		4.7			
2 (12%: 88%)	1.95	1.97	4.7	4.7	2.35	39.97
	1.99		4.8			
	1.98		4.6			
3 (18%: 82%)	1.99	1.99	4.5	4.43	2.22	41.87
	2		4.3			
	1.99		4.5			
4 (24%:76%)	2	1.99	4.2	4.13	2.1	43.45
	1.99		4.0			
	2		4.2			
5 (30 %: 70%)	2	2.03	4.2	4.1	2.05	44.71
	2.1		4.0			
	2		4.0			

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4.1.1.4 Results of the Ratios of Amlodipine Set-1:

4.1.1.4.1 Carr's Index and Hausner's Ratio Measurement for the Ratios of Amlodipine Set1:

Table-4.7: Carr's index and Hausner ratio measured for Amlodipine Set-1.

Ratio	Bulk Volume, Vo (ml)	Most Acceptable Value of Vo (ml)	Tapped Volume, V_f (ml)	Most Acceptable value of V_f	Hausner's Ratio	Compressibility index (%)
1 (3%: 97%)	3.0 2.9 3.0	3.0	2.4 2.5 2.4	2.4	1.25	20
2 (5%: 95%)	3.3 3.3 3.2	3.3	2.40 2.40 2.50	2.40	1.38	27.27
3 (7%: 93%)	3.5 3.3 3.3	3.5	2.50 2.70 2.70	2.50	1.40	28.57
4 (9%: 91%)	3.9 3.8 3.5	3.90	2.7 2.80 3.00	2.70	1.44	30.77
5 (11%:89%)	3.9 3.8 3.8	3.90	2.6 2.8 2.8	2.6	1.5	33.33

4.1.1.4.2 Angle of Repose Measurement for the Ratios of Amlodipine Set-1.

Table-4.8: Angle of repose measured for the ratios of Amlodipine Set-1.

Ratio (containing amlodipine)	**Height (h)**	**AVr Height (h)**	**Diameter (2r)**	**AVr Diameter (2r)**	**Radius (r)**	**Angle of Repose (o)**
1 (3%: 97%)	0.8 0.7 0.9	0.8	2 2.1 1.9	2	1	38.66
2 (5%: 95%)	0.9 1 1	0.97	2 2 1.9	1.97	0.99	44.41
3 (7%: 93%)	1.2 1.2 1.1	1.16	2.1 2.0 2.0	2.03	1.02	48.67
4 (9%: 91%)	1.4 1.3 1.4	1.36	2.3 2.3 2.2	2.27	1.13	50.28
5 (11%: 89%)	1.6 1.8 1.5	1.63	2.4 2.3 2.3	2.33	1.16	54.56

Determination of flow property of amlodipine and propranolol against different ratio of CMC

4.1.1.5 Results of the Ratios of the Amlodipine Set-2:

4.1.1.5.1 Carr's Index and Hausner's Ratio Measurement for the Ratios of Amlodipine Set2

Table-4.9:Carr's index and Hausner ratio measured for Amlodipine Set-2.

Ratio With Amlodipine	**Bulk Volume, Vo (ml)**	**Most Acceptable Value of Vo (ml)**	**Tapped Volume, V_f (ml)**	**Most Acceptable value of V_f**	**Hausner's Ratio**	**Compressibility index (%)**
1 (4%: 96%)	3.1 3.0 3.0	3.1	2.50 2.40 2.40	2.4	1.29	22.58
2 (8%: 92)	3.3 3.3 3.2	3.30	2.30 2.50 2.3	2.30	1.43	30
3 (12%: 88%)	3.5 3.5 3.6	3.60	2.5 2.5 2.6	2.50	1.44	30.56
4 (16%: 84%)	3.5 3.8 3.8	3.8	2.7 2.8 2.5	2.5	1.52	34.21
5 (20%: 80%)	3.9 3.5 3.8	3.9	2.5 2.7 2.7	2.50	1.56	35.89

4.1.1.5.2 Angle of Repose Measurement forthe Ratios of Amlodipine Set-2.

Table-4.10: Angle of repose measured for the ratios of Amlodipine Set-2.

Ratio (containing amlodipine)	Height (h)	Average Height (h)	Diameter (2r)	Average Diameter (2r)	Radius (r)	Angle of Repose (o)
1 (4%: 96%)	0.9	0.83	2.1	2.1	1.05	38.33
	0.8		2.0			
	0.8		2.2			
2 (8%: 92%)	1.0	1.03	2.4	2.33	1.17	41.36
	1.1		2.3			
	1.0		2.3			
3 (12%: 88%)	1.2	1.17	2.3	2.26	1.13	45.99
	1.2		2.3			
	1.1		2.2			
4 (16%: 84%)	1.4	1.27	2.2	2.16	1.08	49.62
	1.3		2.2			
	1.1		2.1			
5 (20%: 80%)	1.5	1.43	2.0	2.03	1.02	54.50
	1.4		2.0			
	1.4		2.1			

Determination of flow property of amlodipine and propranolol against different ratio of CMC

4.1.1.6 Results of the Ratios of the Amlodipine Set-3:

4.1.1.6.1 Carr's Index and Hausner's Ratio Measurement for the Ratios of Amlodipine Set3

Table-4.11:Carr's index and Hausner ratio measured for Amlodipine Set-3.

Ratios With Amlodipine	Bulk Volume, Vo (ml)	Most Acceptable Value of Vo (ml)	Tapped Volume, V_f (ml)	Most Acceptable value of V_f	Hausner's Ratio	Compressibility index
1 (6%: 94%)	3.2 3.1 3.1	3.2	2.2 2.3 2.3	2.20	1.45	31.25
2 (12%: 88%)	3.7 3.5 3.5	3.7	2.7 2.5 2.6	2.5	1.48	32.43
3 (18%: 82%)	3.8 3.5 3.8	3.8	2.5 2.7 2.7	2.5	1.52	34.21
4 (24%: 76%)	3.9 4 4	4	2.6 2.8 2.8	2.6	1.53	35
5 (30%: 70%)	4.1 4.3 4.0	4.2	2.7 2.8 2.8	2.7	1.59	35.71

4.1.1.6.2 Angle of Repose Measurement forthe Ratios of Amlodipine Set-3.

Table-4.12: Angle of repose measured for the ratios of Amlodipine Set-3.

Ratio (containing amlodipine)	Height (h)	Average Height (h)	Diameter (2r)	Average Diameter (2r)	Radius (r)	Angle of Repose (o)
1 (6%: 94%)	1.0 0.9 1.0	0.97	2.3 2.3 2.2	2.27	1.14	40.39
2 (12%: 88%)	1.2 1.1 1.0	1.10	2.2 2.3 2.2	2.23	1.12	44.48
3 (18%: 82%)	1.4 1.2 1.2	1.27	2.1 2.0 2.2	2.10	1.05	50.42
4 (24%: 76%)	1.4 1.2 1.3	1.30	2.0 2.0 2.1	2.03	1.02	51.88
5 (30%: 70%)	1.4 1.3 1.3	1.33	2.0 2.0 1.9	1.97	0.98	53.61

Determination of flow property of amlodipine and propranolol against different ratio of CMC

4.1.1.7 Results of the Ratios of Propranolol Set-1:

4.1.1.7.1 Carr's Index and Hausner's Ratio Measurement for the Ratios Propranolol Set-1:

Table-4.13: Carr's index and Hausner ratio measured for Propranolol Set-1.

Ratio (Containing Propranolol HcCl)	**Bulk Volume, Vo (ml)**	**Most Acceptable Value of Vo (ml)**	**Tapped Volume, V_f (ml)**	**Most Acceptable value of V_f**	**Hausner's Ratio**	**Compressibility index**
1 (3%: 97%)	3.1 3.0 3.0	3.1	2.4 2.50 2.50	2.40	1.29	22.58
2 (5%: 95%)	3.2 3.1 3.1	3.2	2.40 2.50 2.50	2.40	1.33	25
3 (7%: 93%)	3.0 3.2 3.2	3.2	2.3 2.50 2.50	2.30	1.39	28.13
4 (9%: 91%)	3.5 3.7 3.5	3.7	2.6 2.8 2.8	2.6	1.42	29.73
5 (11%: 89%)	3.7 3.8 3.8	3.80	2.6 2.7 2.6	2.6	1.46	31.58

Determination of flow property of amlodipine and propranolol against different ratio of CMC

4.1.1.7.2 Angle of Repose Measurement forthe Ratios of Propranolol Set-1.

Table-4.14: Angle of repose measured for the ratios of Propranolol Set-1.

Ratio (containing Propranolol HCl)	Height (h)	AVr Height (h)	Diameter (2r)	AVr Diameter (2r)	Radius (r)	Angle of Repose (o)
1 (3%: 97%)	0.9	0.83	2.0	1.97	0.99	39.98
	0.8		2.0			
	0.8		1.9			
2 (5%: 95%)	1.0	1.07	1.9	1.93	0.97	47.80
	1.1		1.9			
	1.1		2.0			
3 (7%: 93%)	1.2	1.13	2.0	1.87	0.93	50.54
	1.1		1.8			
	1.1		1.8			
4 (9%: 81%)	1.2	1.17	1.8	1.87	0.93	51.52
	1.2		1.8			
	1.1		2.0			
5 (11%: 89%)	1.4	1.33	1.8	1.83	0.91	55.62
	1.3		1.8			
	1.3		1.9			

4.1.1.8 Results of the Ratios of the Propranolol Set-2:

4.1.1.8.1 Carr's Index and Hausner's Ratio Measurement for the Ratios of Propranolol Set-2

Table-4.15: Carr's index and Hausner ratio measured for Propranolol Set-2.

Ratio With Amlodipine	Bulk Volume, Vo (ml)	Most Acceptable Value of Vo (ml)	Tapped Volume, V_f (ml)	Most Acceptable value of V_f	Hausner's Ratio	Compressibility index
1 (4%: 96%)	3.3 3.0 3.1	3.1	2.50 2.60 2.60	2.5	1.24	19.35
2 (8%: 92%)	3.3 3.5 3.5	3.5	2.60 2.70 2.60	2.60	1.35	25.71
3 (12%: 88%)	3.5 3.5 3.8	3.80	2.8 2.9 2.9	2.8	1.36	26.31
4 (16%: 84%)	3.5 3.8 3.8	3.80	2.7 2.9 2.9	2.7	1.41	28.95
5 (20%: 80%)	4.0 3.9 3.9	4.0	2.8 3.0 3.0	2.8	1.43	30

4.1.1.8.2 Angle of Repose Measurement forthe Ratios of Propranolol Set-2.

Table-4.16: Angle of repose measured for the ratios of Propranolol Set-2.

Ratio (containing propanolol)	Height (h)	Average Height (h)	Diameter (2r)	Average Diameter (2r)	Radius (r)	Angle of Repose (o)
1 (4%: 96%)	0.9 0.9 0.8	0.87	2.1 2.1 2.2	2.13	1.07	39.11
2 (8%: 92%)	1.0 0.9 0.9	0.93	2.1 2.0 2.0	2.03	1.02	42.36
3 (12%: 88%)	1.1 1.0 1.0	1.03	2.0 2.0 2.0	2.03	1.02	44.28
4 (16%: 84%)	1.1 1.2 1.2	1.17	1.9 2.0 1.9	1.93	0.97	50.34
5 (20%: 80%)	1.3 1.1 1.3	1.23	1.9 1.9 1.8	1.87	0.93	52.91

Determination of flow property of amlodipine and propranolol against different ratio of CMC

4.1.1.9 Results of the Ratios of the Propranolol Set-3:

4.1.1.9.1 Carr's Index and Hausner's Ratio Measurement for the Ratios of Propranolol Set3

Table-4.17: Carr's index and Hausner ratio measured for Propranolol Set-3.

Ratios With (Propranolol HCl)	**Bulk Volume, Vo (ml)**	**Most Acceptable Value of Vo (ml)**	**Tapped Volume, V_f (ml)**	**Most Acceptable value of V_f**	**Hausner's Ratio**	**Compressibility index**
1 (6%: 94%)	3.3 3.2 3.3	3.3	2.7 2.8 2.8	2.7	1.29	18.18
2 (12%: 88%)	3.5 3.3 3.4	3.5	2.8 2.9 2.6	2.6	1.35	25.71
3 (18%: 82%)	3.6 3.7 3.7	3.70	2.7 3.00 3.00	2.7	1.37	27.02
4 (24%: 76%)	3.7 3.8 3.9	3.9	2.8 2.9 2.8	2.8	1.39	28.21
5 (30%: 70%)	4.0 4.2 3.8	4.2	3 3.1 3.1	3.0	1.40	28.57

Determination of flow property of amlodipine and propranolol against different ratio of CMC

4.1.1.9.2 Angle of Repose Measurement forthe Ratios of Propranolol Set-3.

Table-4.18: Angle of Repose Measured For The Ratios of Propranolol Set-3.

Ratio (containing amlodipine)	Height (h)	Avr Height (h)	Diameter (2r)	Avr Diameter (2r)	Radius (r)	Angle of Repose (o)
1 (6%: 94%)	1.0 0.9 0.9	0.93	2.3 2.2 2.3	2.27	1.13	39.45
2 (12%: 88%)	0.9 1.0 1.0	0.97	2.2 2.2 2.2	2.2	1.1	41.41
3 (18%: 82%)	1.0 1.0 1.0	1.00	2.1 2.0 2.0	2.03	1.02	44.43
4 (24%: 76%)	1.2 1.0 1.1	1.1	2.0 2.0 2.0	2.0	1.0	47.73
5 (30%: 70%)	1.2 1.1 1.1	1.13	2.1 1.9 2.0	2.0	1.0	48.49

Determination of flow property of amlodipine and propranolol against different ratio of CMC

4.2 Comparison shown using graph among 3 types (excipients, amlodipine, propranolol) of Sets (Set-1, Set-2, Set-3) on the basis of Carr's Index, Hausner Ratio and Angle of Repose

By plotting percentage ratio of CMC 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.

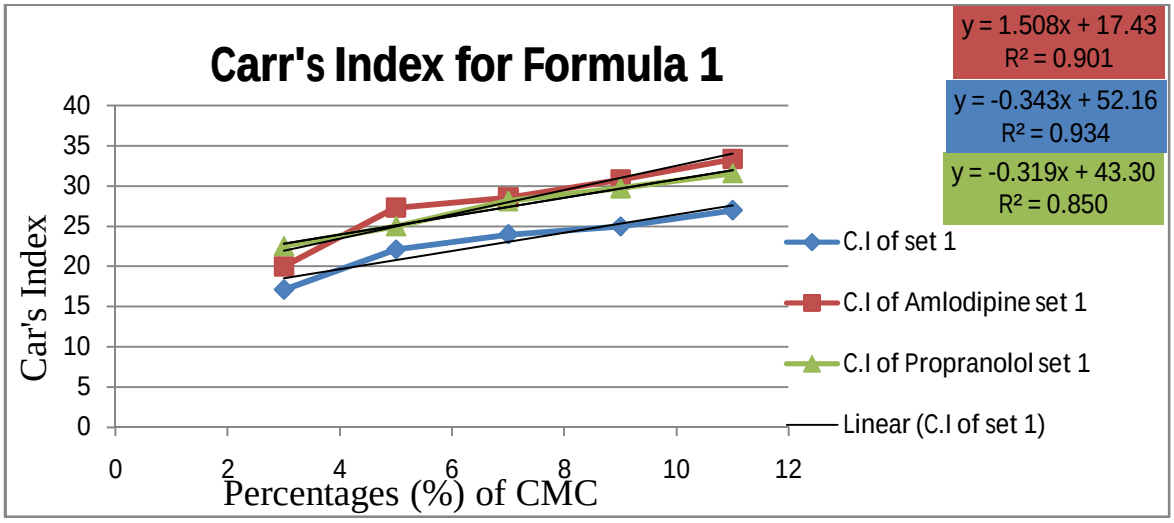
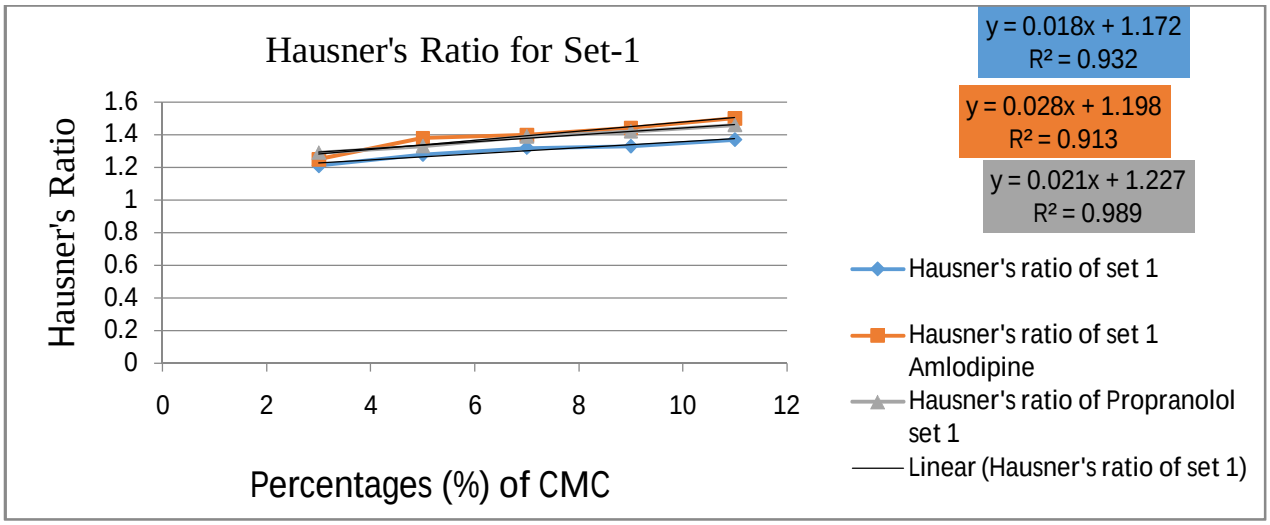


Fig 4.1: A percentage ratio of CMC versus Carr's Index graph

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



Determination of flow property of amlodipine and propranolol against different ratio of CMC

Fig 4.2: A percentage ratio of CMC versus Hausner's Index graph

By plotting percentage ratio of CMC 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.

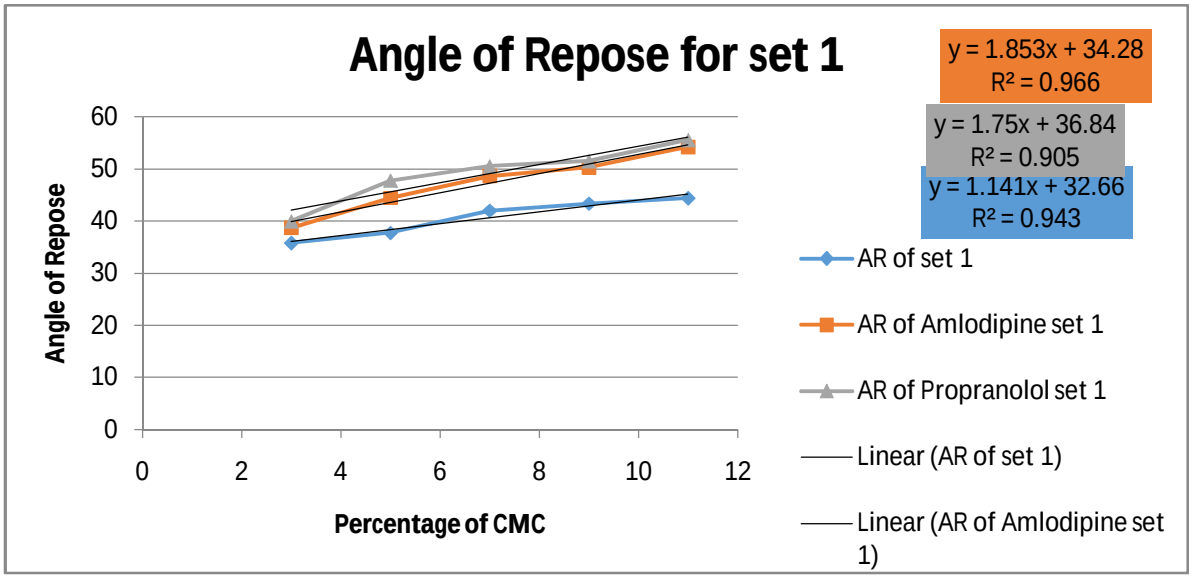


Fig 4.3: A percentage ratio of CMC versus Angle of Repose Index graph

By plotting percentage ratio of CMC 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.

Determination of flow property of amlodipine and propranolol against different ratio of CMC

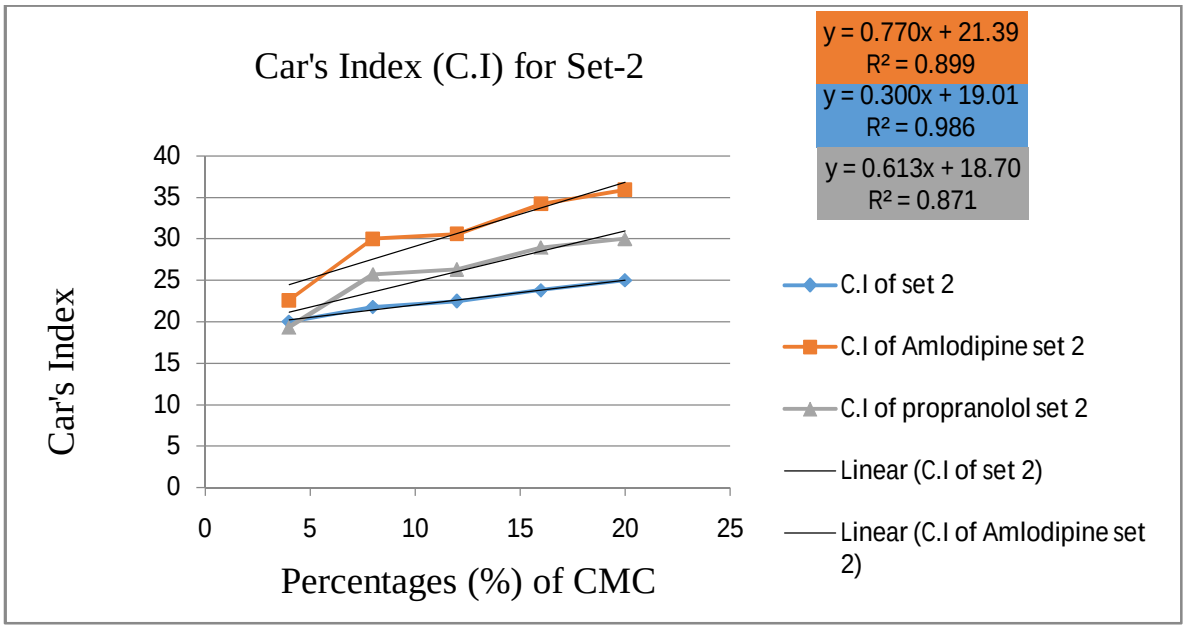


Fig 4.4: A percentage ratio of CMC versus Carr's Index graph

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

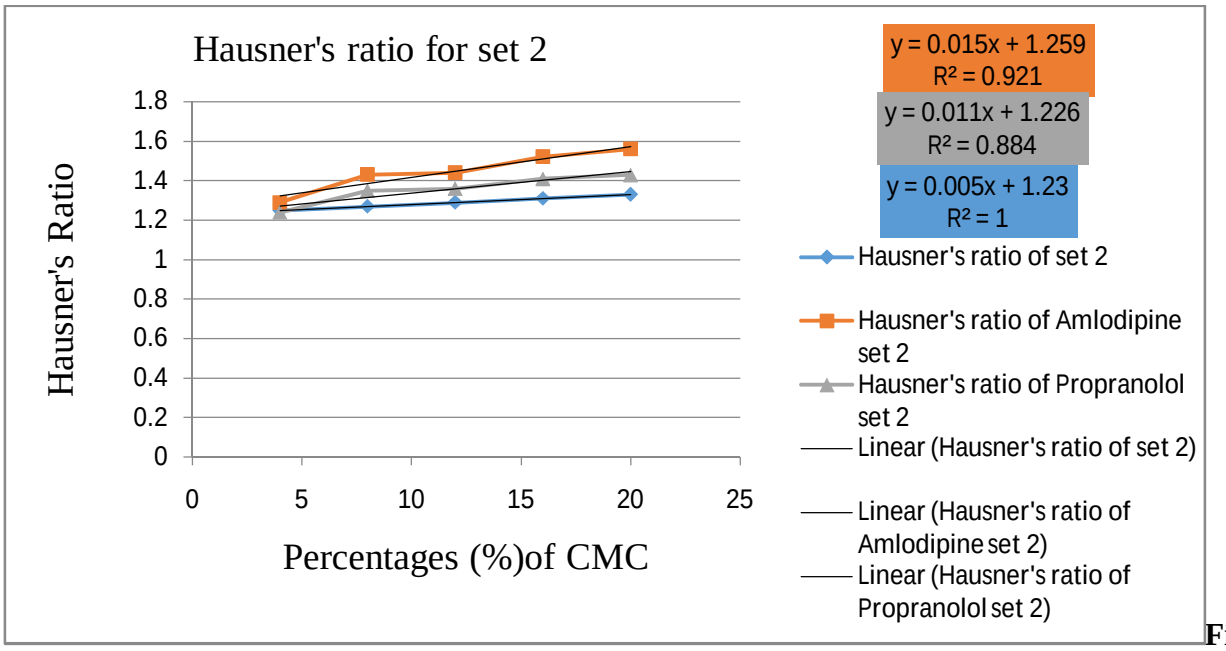


Fig 4.5: A percentage ratio of CMC versus Hausner's Index graph

Determination of flow property of amlodipine and propranolol against different ratio of CMC

By plotting percentage ratio of CMC 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.

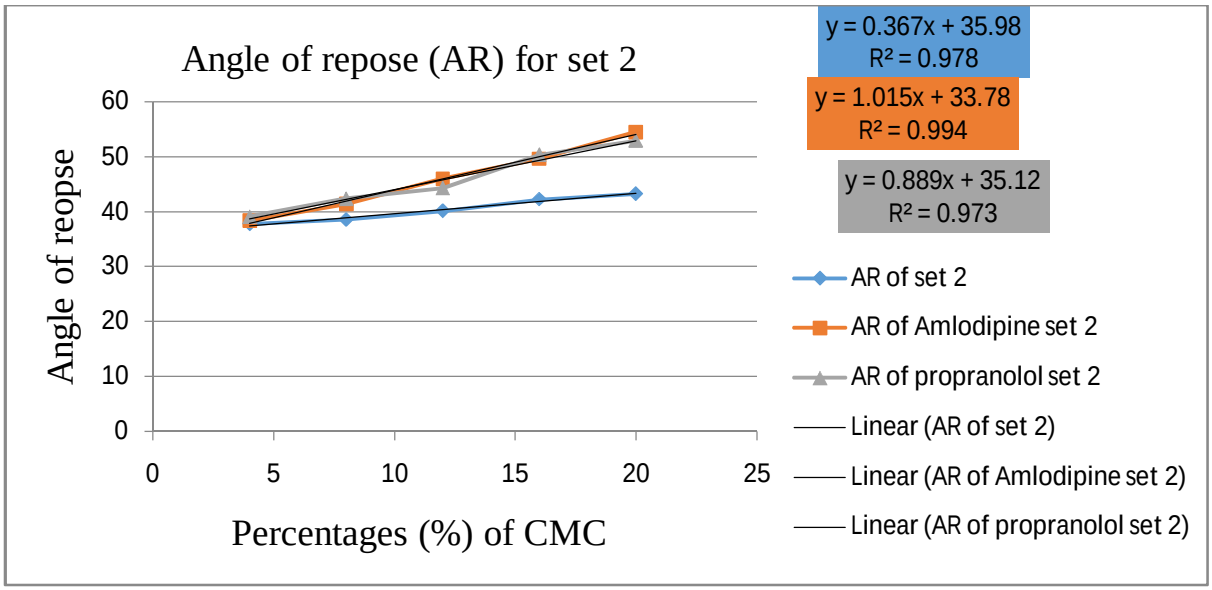


Fig 4.6: A percentage ratio of CMC versus Angle of Repose Index graph

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

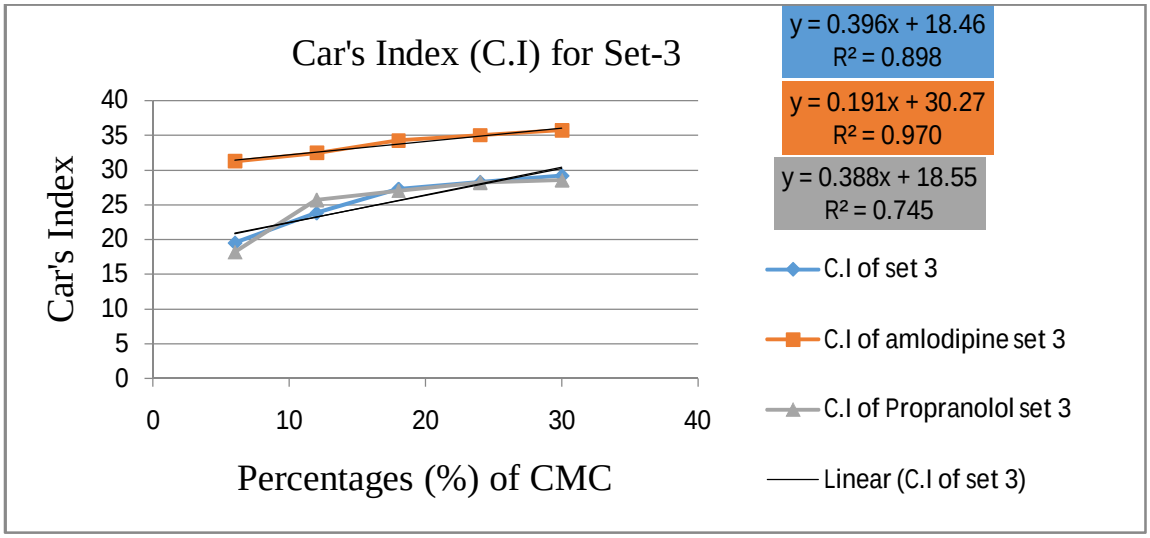


Fig 4.7: A percentage ratio of CMC versus Carr's Index graph

Determination of flow property of amlodipine and propranolol against different ratio of CMC

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

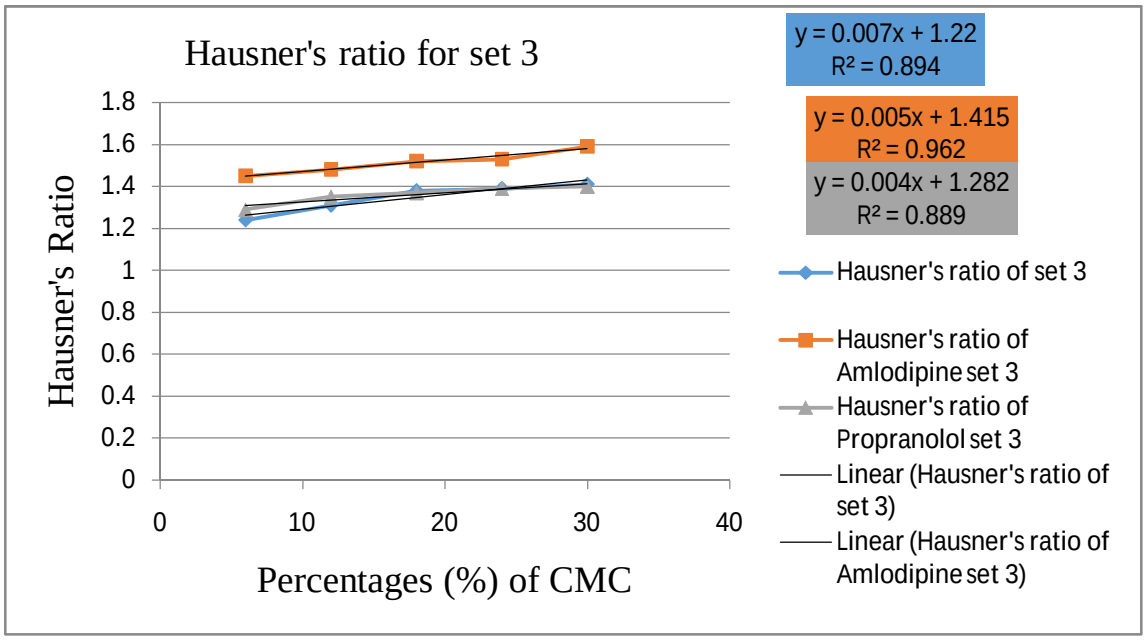


Fig 4.8: A percentage ratio of CMC versus Hausner's Index graph

By plotting percentage ratio of CMCin X-axis and respected Hausner ratio in Y-axis, a graph is plotted by which and equation and regression value was established. Using these

Determination of flow property of amlodipine and propranolol against different ratio of CMC

equations,Hausner's ratio of any set of excipients and APIs can be achieved.

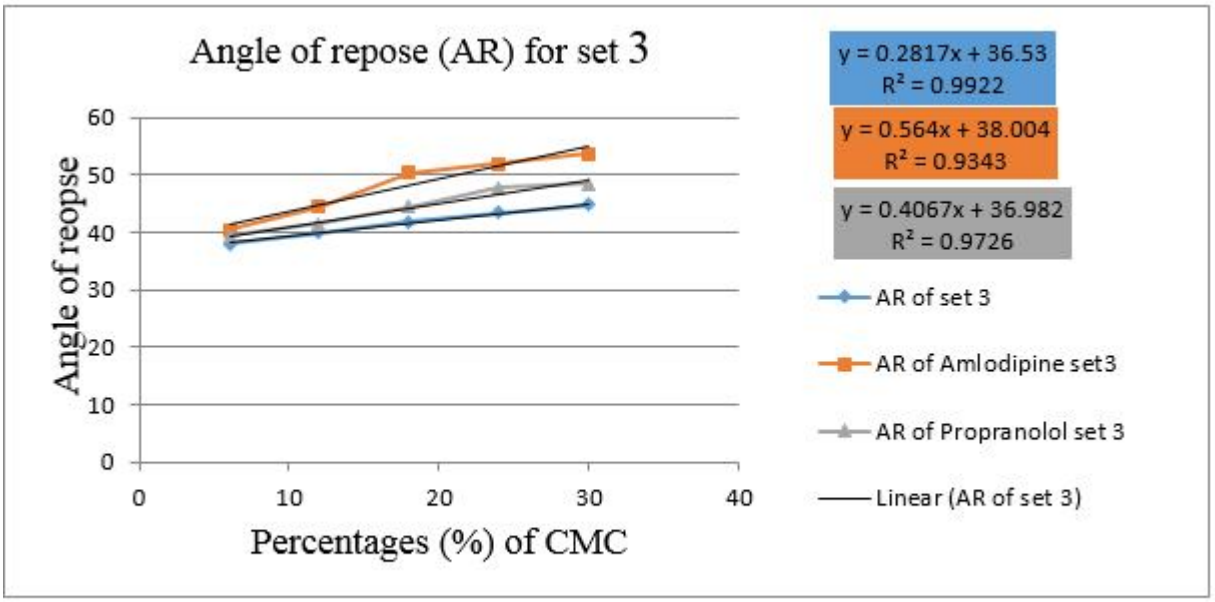


Fig 4.9: A percentage ratio of CMC versus Angle of Repose Index graph

4.3 Equation and regression value of graph

4.3.1: Equation and regression value for Carr's index

Carr's Index	Equation and Regression value
Set-1	y = -0.343x + 52.16 R^2 = 0.934…(i)
Set-2	y = 0.3005x + 19.014 R^2 = 0.9863…(ii)
Set-3	y = 0.3965+ 18.465 R^2 = 0.898....(iii)
Amlodipine with set-1	y = 1.508x + 17.432 R^2 = 0.9012….(iv)
Amlodipine with set-2	y = 0.7707x + 21.399 R^2 = 0.8993…(v)
Amlodipine with set-3	y = 0.1915+ 30.273 R^2 = 0.9705…(vi)
Propranolol with set-1	y = -0.319x + 43.30 R^2 = 0.850….(vii)
Propranolol with set-2	y = 0.613x + 18.702 R^2 = 0.8717….(viii)
Propranolol with set-3	y = 0.388x + 18.554 R^2 = 0.7455….(ix)

Determination of flow property of amlodipine and propranolol against different ratio of CMC

4.3.2Equation and regression value for Hausner's ratio

Hausner's Ratio	Equation and Regression value
Set-1	$y = 0.0185x + 1.1725$ $R^2 = 0.9326$….(i)
Set-2	$y = 0.005x + 1.23$ $R^2 = 1$….(ii)
Set-3	$y = 0.007x + 1.22$ $R^2 = 0.8945$….(iii)
Amlodipine with set-1	$y = 0.028x + 1.198$ $R^2 = 0.9138$….(iv)
Amlodipine with set-2	$y = 0.0158x + 1.259$ $R^2 = 0.9213$…..(v)
Amlodipine with set-3	$y = 0.0055x + 1.415$ $R^2 = 0.962$……(vi)
Propranolol with set-1	$y = 0.0215x + 1.2275$ $R^2 = 0.9898$….(vii)
Propranolol with set-2	$y = 0.011x + 1.226$ $R^2 = 0.8848$….(viii)
Propranolol with set-3	$y = 0.0043x + 1.282$ $R^2 = 0.8895$….(ix)

4.3.3Equation and regression value for Angle of Repose

Angle of Repose	Equation and Regression value
Set-1	$y = 1.1415x + 32.66 R^2 = 0.9435$….(i)
Set-2	$y = 0.367x + 35.984 R^2 = 0.9784$….(ii)
Set-3	$y = 0.2817x + 36.53 R^2 = 0.9922$….(iii)
Amlodipine with set-1	$y = 1.8535+ 34.282 R^2 = 0.9664$ ….(iv)
Amlodipine with set-2	$y = 1.015x + 33.78 R^2 = 0.9948$….(v)
Amlodipine with set-3	$y = 0.564x + 38.004 R^2 = 0.9343$….(vi)
Propranolol with set-1	$y = 1.75x + 36.842 R^2 = 0.9054$….(vii)
Propranolol with set-2	$y = 0.8895x + 35.126 R^2 = 0.9733$….(viii)
Propranolol with set-3	$y = 0.4067x + 36.982 R^2 = 0.9726$….(ix)

Chapter-5:
Discussion

5.1 DISCUSSION

This research was performed to determine the flow properties of different excipients with and without APIs with varying degree of disintegrant CMC. Flow property varied due to different ratios of CMC.Flow property was good when CMC was less in whole mixture. The result might vary because of human error as there was lack of expertise and also for environmental imbalance. I determined the flow property by using some parameters like hausner's ratio, carr's index and angle of repose. The values of Carr's index, Hausner's ratio and angle of repose were plotted against the percentage ratios of disintegrants. From these graphs the straight line equation for each set of formula were obtained which can be used to predict the flow property of these formula with different ratio of disintegrantsand their compatibility with different types of APIs. In this research the straight line equation for APIs were compared with the excipient formula to identify the difference between the two results.

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

Flow property of different formulas can be easily understood from the table 4.3.1 for hausner's ratio. From these equations we can find out any desired flow property. For example, if we consider equation (1) $y = -0.343x + 52.16$ $R^2 = 0.934$ here Y value represents percentage of disintegrant. For any percentage of disintegrant the value for X can be determined with desired R value. Most desirable regression value determined for excipient formula for set-(equation i:$y = 0.007x + 1.22$ $R^2 = 0.8945$) and for amlodipine and propranolol for set-1(equationiv: $y = 1.508x + 17.432$ $R^2 = 0.9012$)and vii:$y = 0.0215x + 1.2275$ $R^2 = 0.9898$)

- In case of set 2 (table 4.3), the most desirable result was observed for 4%:96% (Starch: Formula 2) ratio. For this ratio the range for hausner's ratio and carr's index was in fair range and angle of repose was in fair range. Here the percentage for binder was same in formulation which might be a reason for poor result. As human error was less in this case set 2. Here also the flow ability decreased with increasing degree of disintegrant.The values of amlodipine and propranolol were similar to the excipient values. When the results were plotted into straight line equation all three formulation showed a good result. The result from the equation for both amlodipine and propranolol were increased than the excipient formulation equation.

- In case for set 3, it showed good and both bad results than above two for hausner's ratio, carr's index and angle of repose (table 4.5 and 4.6). The reason behind this might be the ratio of the excipient used. Here percentage of disintegrant was higher than above two formulas. The best result was observed for 6%:94 (Starch: Formula 3) ratio for all the flow ability criteria. In formula 3 the amount of CMC was high, if they were used in lower amount the result might be improved from fair to good as flow properties are increased with decreasing degree of CMC.Here it became poor from fair result as the ratio was increasing.When compared in straight line equation propranolol showed better value than amlodipine but both APIs flow property slightly poor from the excipient formulation.

Chapter-6

Conclusion

6.1 Conclusion

The flow property of different powder during manufacturing indicates the quality of product.The powder flow also affects the manufacturing efficiency. At the time of development of any formulation the flow of powder may affect the selection of excipients whether they can be directly compressed or not.Thats why it is very important to know the flow property of powder for the manufacturing of solid pharmaceutical dosage forms. Powders with better flow property will give advantages in manufacturing of directly compressed solid dosage forms. Because excipients are used in a larger portion in any dosage forms. This experiment was done to find out several equation for various ratios of CMC.These equations will help the future researchers and pharmaceutical personnel to predict and determine the flow ability of mixtures for adding the CMC which may help to save money and time. Further research works on this property will be helpful.

Chapter 7:
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