"FORMULATION DEVELOPMENT AND EVALUATION OF IMMEDIATE RELEASE FIXED DOSE COMBINATION OF ANTI-HYPERTENSIVE AGENTS"

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In Partial Fulfillment for the Award of the Degree of

MASTER OF PHARMACY

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PHARMACEUTICAL TECHNOLOGY &

BIOPHARMACEUTICS

BY

RISHIKUMAR GOVINDBHAI PATEL (14MPH118), B. PHARM.

Under the guidance of

Dr. Mayur M. Patel – GUIDE
Associate Professor, Department of Pharmaceutics

Dr. Pavak Mehta – INDUSTRIAL GUIDE
Senior General Manager, F&D, SOD, PTC, Cadila Healthcare Limited, Ahmedabad

Department of Pharmaceutics
Institute of Pharmacy
Nirma University
Ahmedabad-382481
Gujarat, India.

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CERTIFICATE

This is to certify that the dissertation work entitled "Formulation, Development and Evaluation of Immediate Release Fixed Dose Combination of Anti-hypertensive Agents" submitted by Mr. Rishikumar Govindbhai Patel with Regn. No. (14MPH118) in partial fulfillment for the award of Master of Pharmacy in "Pharmaceutical Technology and Biopharmaceutics" is a bonafide research work carried out by the candidate at the Department of Pharmaceutics, Institute of Pharmacy, Nirma University and at Formulation & Development Department, Solid Oral Department, Pharmaceutical Technology Center, Cadila Healthcare LTD, Moraiya, Ahmedabad under our guidance. This work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

Industrial Guide

Dr. Pavak Mehta,
Senior General Manager,
F&D, Solid Oral Dept., PTC,
Cadila Healthcare LTD,
Moraiya, Ahmedabad.

Academic Guide:

Dr. Mayur M. Patel
M. Pharm., Ph.D.,
Associate Professor,
Department of Pharmaceutics,
Institute of Pharmacy,
Nirma University

23/5/2016

Prof. Manjunath Ghate
M. Pharm., Ph.D.
Director,
Institute of Pharmacy,
Nirma University

Prof. Tejal Mehta
M. Pharm., Ph.D.,
Professor & Head,
Department of Pharmaceutics,
Institute of Pharmacy,
Nirma University

Date: 20th May, 2016

DECLARATION

I hereby declare that the dissertation entitled "Formulation, Development and Evaluation of Immediate Release Fixed Dose Combination of Anti-hypertensive Agents", is based on the original work carried out by me under the guidance of Dr. Mayur M. Patel, Associate Professor, Department of Pharmaceutics, Nirma University and Dr. Pavak Mehta, Senior General Manager, F&D, OSD, PTC, Cadila Healthcare LTD. I also affirm that this work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

Mr. Rishikumar G. Patel (14MPH118)
Department of Pharmaceutics,
Institute of Pharmacy,
Nirma University,
Sarkhej - Gandhinagar Highway,
Ahmedabad-382481,
Gujarat, India

Date: 20th May, 2016

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List of Abbreviations

Sr. No.	Short Form	Abbreviations
1	AHD X	Anti-hypertensive Drug X
2	AHD Y	Anti-hypertensive Drug Y
S3	IR	Immediate Release
4	API	Active Pharmaceutical Ingredient
5	UV	Ultra Violet
6	HCL	Hydrochloric Acid
7	MCC	Microcrystalline Cellulose
8	FT-IR	Fourier transform infrared spectroscopy
9	RH	Relative Humidity
10	CCS	Croscarmellose Sodium
11	SLS	Sodium Lauryl Sulphate
12	PVP K30	Polyvinylpyrrolidone K30
13	LHPC LH11	Low-substituted Hydroxypropyl Cellulose
14	HPLC	High Performance Liquid Chromatography

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"Formulation Development and Evaluation of Immediate Release Fixed Dose Combination of Anti-hypertensive Agents"

The occurrence of hypertension is high in the patients with different of diseases like diabetes mellitus, chronic kidney disease and chronic cardiovascular disease. In addition, these subjects have the lowest control of blood pressure (BP) among the hypertensive patients and also the risk having a morbid or fatal cardiovascular event>20% in 10 years. For these reasons, the aggressive control of BP to <130/80 mm Hg for these subjects is strongly recommended by National and International guidelines. To achieve this goal, combination therapy is used with two or more anti-hypertensive drugs with a complementary mechanism of action is necessary. Drugs that block renin-angiotensin system RAS (Angiotensin II Type 1 receptor blockers) in combination with a calcium channel blocker (CCB) have been shown to be the most effective combinations. Several studies have shown that patient compliance is related to the number of drug is administered. Sometimes, multiple drugs given separately decrease patient compliance and adherence to the treatment. To overcome these problems, different dual and triple drug fixed dose combination of Anti-hypertensive drugs being administered. Which are effective, safe and well tolerated by the patients. Here, the combination of class I and class II drugs are formulated and developed by using two different methods such as Wet Granulation method & Dry Granulation method. In which the different concentration of binders, disintegrants and solubilizers were added into intragranuler part or extragranuler part. In the coating of tablet, OPADRY ® Orange (HPMC Based) was used. The coated tablets were evaluated for assay, weight variation, disintegration time, % friability, hardness, drug content and in vitro drug release. The formula was optimized to generate the formulation which gives same drug release profile as that of innovator formulation. Thus the final formula was optimized for effective fixed dose combination of Anti-hypertensive agents.

1. Aim of Present Investigation

1.1 Rationale for selection of Dosage form

Oral delivery is currently the most popular in the pharmaceutical industry where it is regarded as the safest, most convenient and most economical method of drug delivery having the highest patient compliance. The tablet and capsules are the most widely used dosage form because of its convenience in terms of self administration, do not require sterile conditions and are therefore, less expensive to manufacture, good stability high-precision dosing and ease in manufacturing. Formulation of a convenient dosage form like a Tablet for oral administration, by considering swallowing difficulty especially in case of geriatric and paediatric patient leads to poor patient compliance.

Fixed dose combination of antihypertensive agents useful in controlling class I and class II hypertension. Fixed-dose combinations of antihypertensive agents were associated with increased compliance and no changes in the frequency of adverse events when compared with free drug components given separately. Interest in the effect of the circadian rhythm of blood pressure in terms of its association with the occurrence of cardiovascular events posits the question as to whether single- pill, fixed-dose combinations may provide greater benefit when administered at bedtime.

Calcium antagonists are powerful, intrinsically natriuraemic, vasodilators resulting in a negative sodium balance and the stimulation of the renin-angiotensin-aldosterone system (RAAS), while angiotensin receptor blockers (ARBs) and angiotensin converting enzyme (ACE) inhibitors, in contrast, block the RAAS, and, if administered in combination with calcium antagonists, in fact enhance their antihypertensive effects. Combination therapy is well tolerated and is associated with a lower incidence of side effects, such as oedema, compared to mono therapy

- Immediate release of drug and increased bioavailability.
- Ease of ingestion, versatility (to accommodate various types of drug candidates) and most importantly, patient compliance.
- Any pregastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo first pass hepatic metabolism.

- Patients have special drug administration requirements as they are often unable to swallow solid dosage forms (e.g. tablets, capsules).
- Avoid of taking two different drug individual.
- Once a day dose easy to administration and patient compliance.
- Dose not affect with and without food effect.
- Pregestric absorbtion avoid fist pass metabolism which is essentially useful in
- AHD having 26% bioavailability due to drastic metabolism in hepatic route.
- Both drug are BCS class Iand II drug, so drug release is rate determining step of drug action. Thus immediate release tablet is necessary.
- AHD Y extensively metabolite in hepatic metabolism which reduce in immediate release drug delivery system.
- Both drug highly protein bound drug so produce once a day dose with sustain effect.

1.2. Rationale for selection of Drug

- AHD X and AHD Y are highly protein bound drug, so they remain in the body& produce prolong effect.
- Both drug in combination is produce additive effect.
- Both drug are class II drugs having low solubility, so solubility of drug is important parameter for determining pharmacological property.
- Both drug are does not cross BBB so does not produce serious neurotoxicity.
- AHD X having only 26% bioavaibility due to degradation in hepatic region.
- Immediate drug delivery enhance absorbance of drug.
- AHD Y having $t_{1/2}$ is 20~30 hr so it produce sustain effect

So, the aim of the present work is **"Formulation, Development and Evaluation of Immediate Release Fixed dose combination of Anti-hypertensive Agents".**

1.3 Objectives:

- To develop swallable immediate release tablet.
- To prepare tablet without using direct compression method.
- To increase solubility of two drug by addition of different solubilizer.
- To produce stable and efficacious drug release product.
- To screening different binder and its concentration to affect drug release.
- To enhance drug release of AHD Y and AHD X.
- To protect drug from moisture by film coating.
- Check the pharmaceutical equivalence of the tablet made by trial & error method with the reference product.
- To carry out physical evaluation like hardness, thickness of tablets, content uniformity, USP disintegration test and chemical evaluation includes in-vitro dissolution studies of the formulated oral controlled release osmotic tablets.
- To compare drug release profile of prepared formulation with marketed formulation.

2. Introduction

2.1. Oral Drug Delivery System[1]

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance.

Oral medication conveyance is the least complex and most straightforward method for controlling medications. In view of the more noteworthy security, littler mass, precise measurements and simple generation, strong oral doses frames have numerous points of interest over different sorts of oral dose shapes. In this way, the greater part of the new compound elements (NCE) a work in progress nowadays are proposed to be utilized as a strong dose frame that begin a compelling and reproducible in vivo plasma focus after oral organization.

2.1.1. Difficulties with Existing Oral Dosage Form

1. Patient may experience the ill effects of tremors hence they experience issues to take powder and fluids. In dysphasia physical snags and adherence to a throat may bring about gastrointestinal ulceration.
2. Gulping of strong measurements frames like tablet and containers and produce trouble for youthful grown-up of deficient advancement of solid and sensory system and elderly patients experience the ill effects of dysphasia.
3. Fluid medicaments (suspension and emulsion) are stuffed in multidisc holder; hence accomplishment of consistency in the substance of every dosage might be troublesome.
4. Buccal and sublingual development may make aggravation oral mucosa, so patients declined to utilize such meds.
5. Expense of items is fundamental variable as parenteral definitions are most excessive and uneasiness.

2.1.2. Problems and Barriers to Oral Drug Delivery

- Physicochemical Barriers to ODD
  - Aqueous solubility
  - Lipophilicity
  - Aqueous boundary layer
- Biological Barriers to ODD
  - Intestinal epithelial barrier
  - Gastrointestinal transit
  - Food effect
- Metabolic and Biochemical Barriers to ODD
  - Presystemic metabolism like lumenal metabolism, first-pass intestinal metabolism, first-pass hepatic metabolism
  - P-Glycoprotein and other efflux systems

2.2. Tablet[2]

Tablets might be characterized as strong pharmaceutical dosage forms containing medicament with or without appropriate excipients and arranged either by pressure or embellishment Despite the long and proceeding with history of the advancement of new advances for organization of medications, the tablet structure remains the most usually utilized dose structure.

The best new helpful substance in the world is of little esteem without a fitting conveyance framework. Tableted drug conveyance frameworks can go from generally straightforward quick –release details to complex expanded or adjusted discharge measurement shapes. The most critical part of a medication conveyance framework is to get the medication "conveyed" to the site of activity in adequate sum and at the suitable rate; in any case, it should likewise meet various other vital criteria.

2.2.1. Properties of an Ideal Tablet[3]

The objective of formulation and fabrication of tablet is to deliver the correct amount of drug in proper form at or over proper time.

- Tablet should be elegant having its own identity and free from defects such as cracks, chips, contamination, discoloration etc.
- It should have chemical and physical stability to maintain its physical integrity overtime.
- It should be capable to prevent any alteration in the chemical and physical properties of medicinal agent(s).
- It should be capable of withstanding the rigors of mechanical shocks encountered in its production, packaging, shipping and dispensing.
- An ideal tablet should be able to release the medicament(s) in body in predictable and reproducible manner.

2.2.2. Advantages of Tablet[3]

- They are unit measurement structure, and they offer the abilities of all oral dose frames for the dosage accuracy and the slightest substance variability amid dosing.
- Accuracy and consistency of medication substance.
- Optimal drug disintegration and thus, accessibility from the measurements structure for assimilation predictable with proposed use (i.e., quick or augmented discharge).
- Usually taken orally, however can be controlled sublingually, rectally or intravaginally.
- Their expense is most minimal of all oral dose frames.
- They are the most minimal of all oral measurements frames.
- They are as a rule the simpler and less expensive to bundle and ship as contrast with other oral measurements frames.
- Product distinguishing proof is straightforward and shabby, requiring no extra preparing strides while utilizing a decorated or monogrammed punch face.
- They are simplicity to control, does not require an authority.
- They are more qualified to vast scale creation than other unit oral structures.
- They have the better properties of concoction, mechanical and microbiological strength.

2.2.3. Disadvantage of Tablet

- Some drugs oppose pressure, because of their formless nature or low-thickness.
- Drugs having severe taste, shocking smell or medications that are delicate to oxygen may require epitome or covering of tablet.
- Bioavailability issues.
- Chance of GI aggravation created by locally high focuses medicament.
- Difficulty in swallowing tablets in a little extent of individuals thus size and shape get to be essential contemplations.
- Slow onset of activity when contrasted with parenteral and arrangements.

2.2.4. Classification of Tablet[3]

1. **Tablets Ingested orally**

- Compressed tablets
- Multiple compressed tablet

➢ Layered tablets

➢ Compression-coated tablets

- Repeat-action tablets
- Delayed-action and enteric-coated tablets
- Sugar and chocolate-coated tablets
- Film coated tablets
- Chewable tablets
- Targeted tablets

➢ Floating tablets

➢ Colon targeted tablets

These tablets are meant to be swallowed intact along with a sufficient quantity of potable water. Exception is chewable tablet. Over 90% of the tablets manufactured today are ingested orally. This shows that this class of formulation is the most popular worldwide and the major attention of the researcher is towards this direction.

2. Tablets Used in the Oral Cavity

- Buckle tablets
- Sublingual tablets
- Troches and lozenges
- Dental cones
- Mouth Dissolving Tablets

The tablets under this gathering are pointed discharge API in oral depression or to give nearby activity in this area. The tablets under this class keeps away from first-pass digestion system, deterioration in gastric environment, sickness tic sensations and gives quick onset of activity. The tablets detailed for this area are intended to fit in legitimate locale of oral cavity.

3. Tablets Administered by Other Routes

- Implantation tablets
- Vaginal tablets

These tablets are managed by other course aside from the oral hole thus the medications are kept away from going through gastro intestinal tract. These tablets might be embedded into other body cavities or specifically set beneath the skin to be retained into systemic flow from the site of use.

4. Tablets Used to Prepare Solutions

- Effervescent tablets
- Dispensing tablets
- Hypodermic tablets
- Tablet triturates

The tablets under this classification are required to be broken up first in water or different solvents before organization or application. This arrangement might be for ingestion or parenteral application or for topical use contingent on kind of medicament utilized.

5. Based on Release

- Immediate drug Delivery

- Controlled drug Delivery
- Targeted drug Delivery System
- Osmatic drug Delivery
- Mouth dissolving / disintegrating drug delivery
- Sublingual / Buckle Tablet
- Mucoadhesive system
- Gastroretantive system

2.3. Introduction to Immediate Release Drug Delivery System

2.3.1. Definition

The term "immediate release" pharmaceutical plan incorporates any detailing in which the rate of arrival of medication from the definition and/or the ingestion of medication, is neither obviously, nor purposefully, impeded by galenic controls.

Immediate release might be accommodated by method for a suitable pharmaceutically worthy diluent or transporter, which diluent or bearer does not delay, to a calculable degree, the rate of medication discharge and/or retention. Hence, the term rejects definitions which are adjusted to accommodate "changed", "controlled", "maintained", "delayed", "amplified" or "deferred" arrival of medication.

2.3.2. Desired Criteria for Immediate Release Drug Delivery System[4,5]

Immediate release dosage form should-In the case of solid dosage it should dissolve Or disintegrate in the stomach within a short period.

1. In the case of liquid dosage form it should be compatible with taste masking.
2. Be portable without fragility concern.
3. Have a pleasing mouth feel.
4. It should not leave minimal or no residue in the mouth after oral administration.
5. Exhibit low sensitivity to environmental condition as humidity and temperature.
6. Be manufactured using conventional processing and packaging equipment at low cost.
7. Rapid dissolution and absorption of drug, which may produce rapid onset of action.

2.3.3. Merits of Immediate Release Drug Delivery System[6,7]

- Improved compliance/added convenience
- Improved stability, bioavailability.
- Suitable for controlled/sustained release actives
- Allows high drug loading.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Adaptable and amenable to existing processing and packaging machinery
- Cost- effective
- Improved solubility of the pharmaceutical composition;
- Decreased disintegration and dissolution times for immediate release oral dosage forms.

2.3.4. Conventional Technique Used in the Preparation of Immediate Release Tablets

1. Direct compression technique
2. Granulation technique
    - **A.** Wet granulation technique
    - **B.** Dry Granulation technique
3. Tablet moulding technique
4. Mass extrusion technique
5. Solid Dispersion technique

1 Direct compression technique[7,8]

The expression "direct compression" is characterized as the procedure by which tablets are packed straightforwardly from powder blend of API and reasonable excipients. No pre-treatment of the powder mix by wet or dry granulation system is required. Amongst the methods used to get ready tablets, direct pressure is the most progressive innovation.

It includes just mixing and pressure, accordingly offering advantage especially as far as expedient generation, as it requires less unit operations, less apparatus decreased number of faculty and significantly less handling time alongside expanded item

dependability.

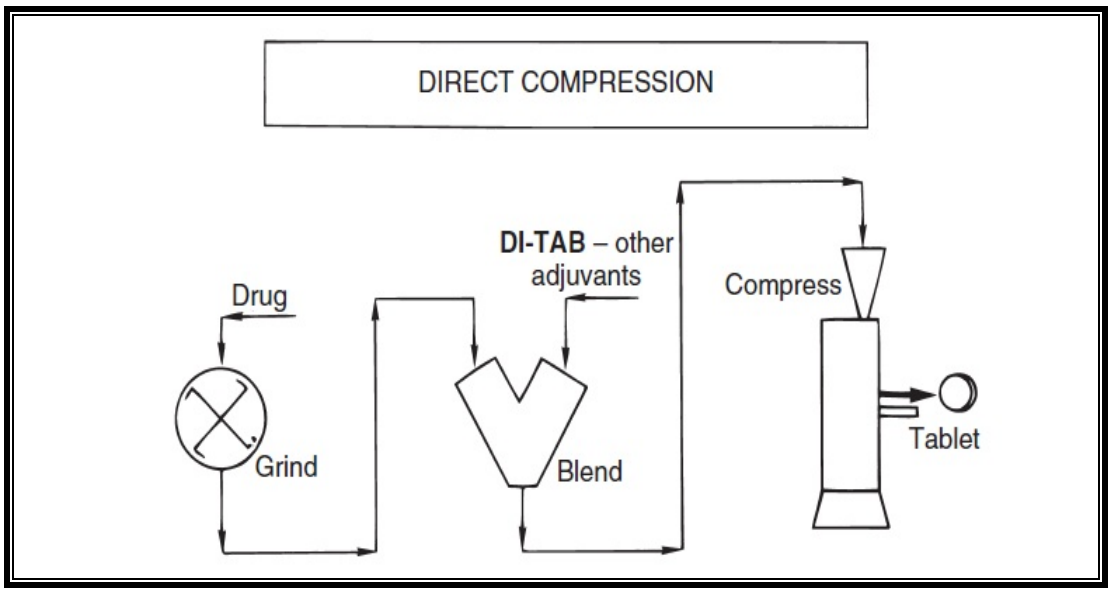


Figure 2.1: Direct Compression Mechanism

Advantages:

- Direct compression is more productive and conservative procedure when contrasted with different procedures, since it includes just dry mixing and compaction of API and fundamental excipients.
- The most critical favorable position of direct pressure is that it is an efficient procedure. Diminished handling time, decreased work costs, less assembling strides, and less number of types of gear is required, less process approval, lessened utilization of force.
- Elimination of warmth and dampness, therefore expanding the strength as well as the appropriateness of the procedure for thermolabile and dampness touchy API.
- Particle size consistency.
- Prime molecule disintegration.
- In instance of straightforwardly packed tablets after deterioration, every essential medication molecule is freed. While on account of tablets arranged by pressure of granules, little medication particles with a bigger surface region follow together into bigger agglomerates; in this manner diminishing the surface territory accessible for disintegration.

Disadvantages:

Excipients Related

- Problems in the uniform circulation of low measurement drugs.
- High dosage drugs having high mass volume, poor compressibility and poor flowability are not appropriate for direct pressure for instance, Aluminum Hydroxide, Magnesium Hydroxide.
- The decision of excipients for direct pressure is to a great degree basic. Direct pressure diluents and fasteners must have both great compressibility and great flowability.
- Many dynamic fixings are not compressible either in crystalline or indistinct structures.

Process Related

- Capping, lamination, splitting, or layering of tablets is sometimes related to air entrapment during direct compression. When air is trapped, the resulting tablets expand when the pressure of tablet is released, resulting in splits or layers in the tablet.
- In some cases require greater sophistication in blending and compression equipments.
- Direct compression equipments are expensive.

In this method, tablets are compressed directly from the mixture of the drug and excipients without any preliminary treatment. The mixture to be compressed must have adequate flow properties and cohere under pressure thus making pretreatment as wet granulation unnecessary. Few drugs can be directly compressed into tablets of acceptable quality. A type of disintegrant and its proportion are of prime importance. The other factors to be considered are particle size distribution, contact angle, pore size distribution, tablet hardness and water absorption capacity. All these factors determine the disintegration. The disintegrant addition technology is cost effective and easy to implement at industrial level.

2 Granulation Technique[9]

Granulation might be characterized as a size extension process which changes over little particles into physically more grounded and bigger agglomerates.

The goal of granulation is to enhance powder stream and taking care of, abatement dustiness, and avoid isolation of the constituents of the item. Granulation technique can be extensively ordered into two sorts:

(i) Wet granulation and

(ii) Dry granulation

Ideal Chracteristics of granules

The perfect attributes of granules incorporate circular shape, littler molecule size appropriation with adequate fines to fill void spaces between granules, satisfactory dampness (between 1-2%), great stream, great compressibility and adequate hardness.

The effectiveness of granulation depends on the following properties:

- Particle size of the drug and excipients
- Type of binder (strong or weak)
- Volume of binder (less or more)
- Wet massing time (less or more)
- Amount of shear applied
- Drying rate (Hydrate formation and polymorphism)

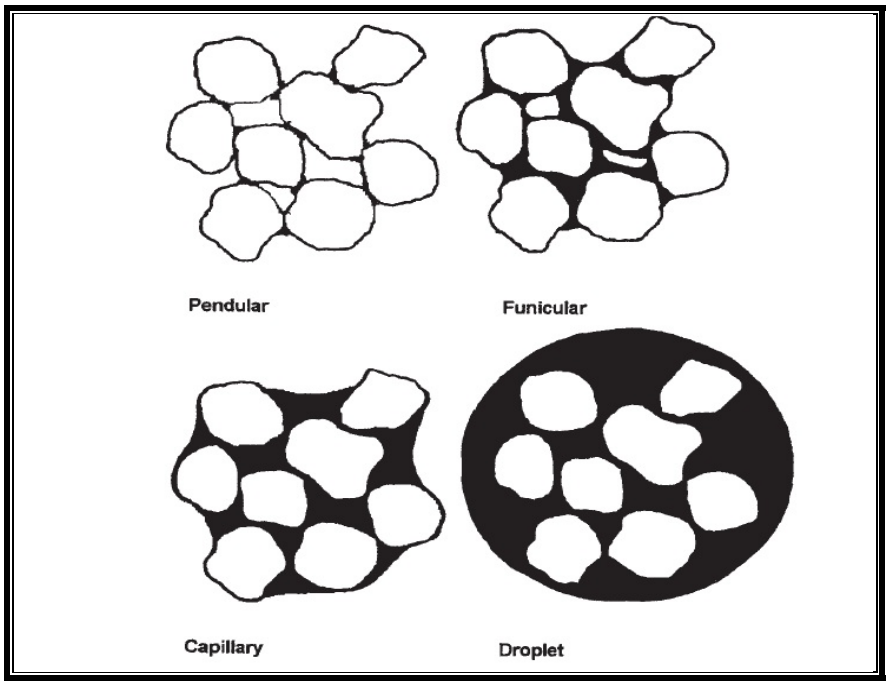


Figure 2.2: Mechanism of granules formation

A. Wet Granulation Technique

Wet granulation is a commonly used unit operation in the pharmaceutical industry. Wet granulation is often carried out utilizing a high-shear mixer.

Low shear wet granulation processes use very simple mixing equipment, and can take a considerable time to achieve a uniformly mixed state. High shear wet granulation processes use equipment that mixes the powder and liquid at a very fast rate, and thus speeds up the manufacturing process. Fluid bed granulation is a multiple-step wet granulation process performed in the same vessel to pre-heat, granulate, and dry the powders. It is used because it allows close control of the granulation process.

The high-shear granulation process is a rapid process which is susceptible for overwetting. In this manner, the fluid sum included is basic and the ideal sum is influenced by the properties of the crude materials. Power utilization of the impeller engine and the impeller torque have been connected to screen the rheological properties of the wet mass amid agglomeration and, in this way, have been utilized to decide the end-purpose of water expansion. Notwithstanding, these techniques are influenced by the hardware variables. Thus, extra process observing procedures would be significant.

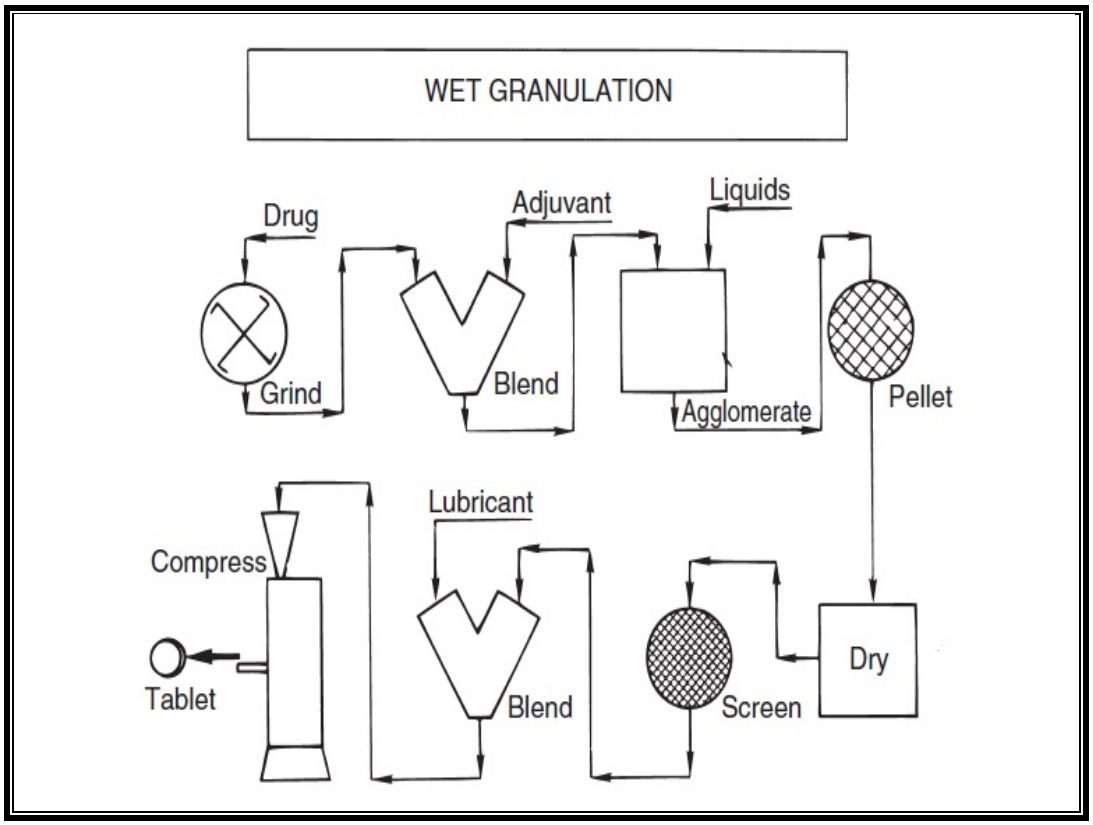


Figure 2.3: Wet Granulation Mechanism

Wet granulation is a procedure of utilizing a fluid fastener to gently agglomerate the powder blend. The measure of fluid must be legitimately controlled, as over-wetting will bring about the granules to be too hard and under-wetting will make them be too delicate and friable.

Fluid arrangements have the upside of being more secure to manage than dissolvable based frameworks yet may not be appropriate for medications which are debased by hydrolysis.

Procedure:

- The dynamic fixing and excipients are weighed and blended.
- The wet crush is set up by adding the fluid binder–adhesive to the powder mix and blending completely. Case of folios/cements incorporate watery arrangements of corn starch, characteristic gums, for example, acacia, and cellulose subordinates, for example, methyl cellulose, gelatin, and povidone.
- Screening the sodden mass through a lattice to shape pellets or granules.

- Drying the granulation. A traditional plate dryer or liquid bed dryer are most normally utilized.
- After the granules are dried, they are gone through a screen of littler size than the one utilized for the wet mass to make granules of uniform size.

Mechanism of Wet granulation

1. Nucleation
2. Transition in the funicular and capillary stage
3. Ball growth.

In nucleation, the formation starts with loose agglomerates or single particles which are wetted by the binding solution and form small granules by pendular bridging.

Continued addition of binding solution and tumbling action consolidates and strengthens the granules through the funicular stage and into the capillary stage.

In this transition stage the granules continue to grow by one of two mechanisms:

(1) Single particle addition and

(2) Multiple granule formation.

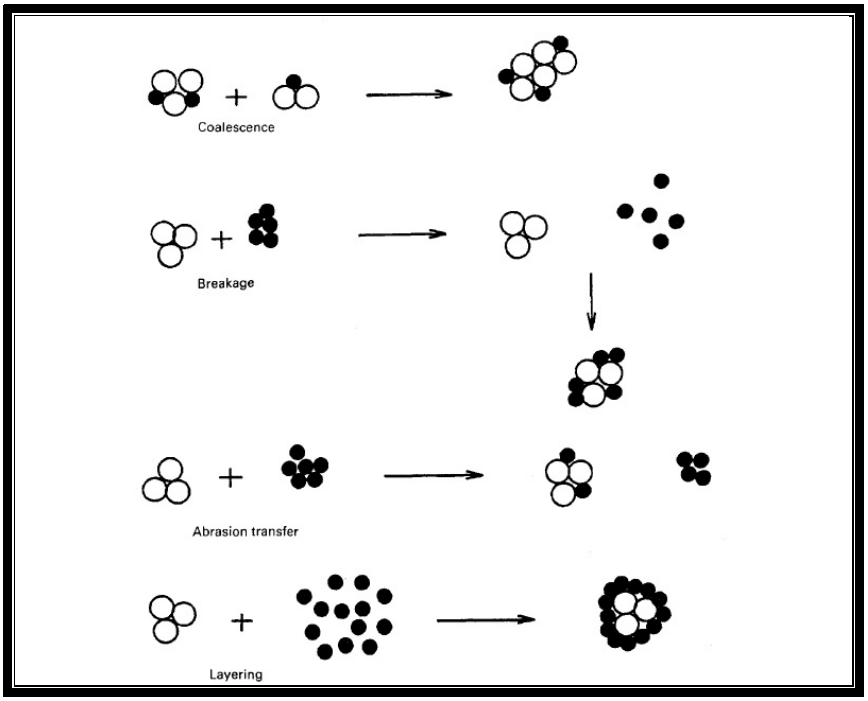


Figure 2.4: Wet Granulation Mechanism

Theoretically, at the end of the transition stage ball formation occur i.e. there are a large number of small granules with a fairly wide size distribution.

Advantages of Wet granulation method:

1. For Low dose drugs, content uniformity in tablets can be increased.
2. Capture and fuse small quantities of active material.
3. Control the tendency of powders to segregate.
4. Improve powder flow.

Limitation of wet granulation:

- The most noteworthy burden of wet granulation is its expense. It is a costly procedure on account of work, time, gear, vitality and space prerequisites.
- Loss of material amid different phases of handling.
- Stability might be a noteworthy sympathy toward dampness delicate or thermolabile medications.
- An innate restriction of wet granulation is that any inconsistency between detailing segments is irritated.

Wet granulation techniques:

- High shear mixture granulation
- Fluid bed granulation
- Extrusion-spheronization
- Spray drying

B. Dry Granulation Technique

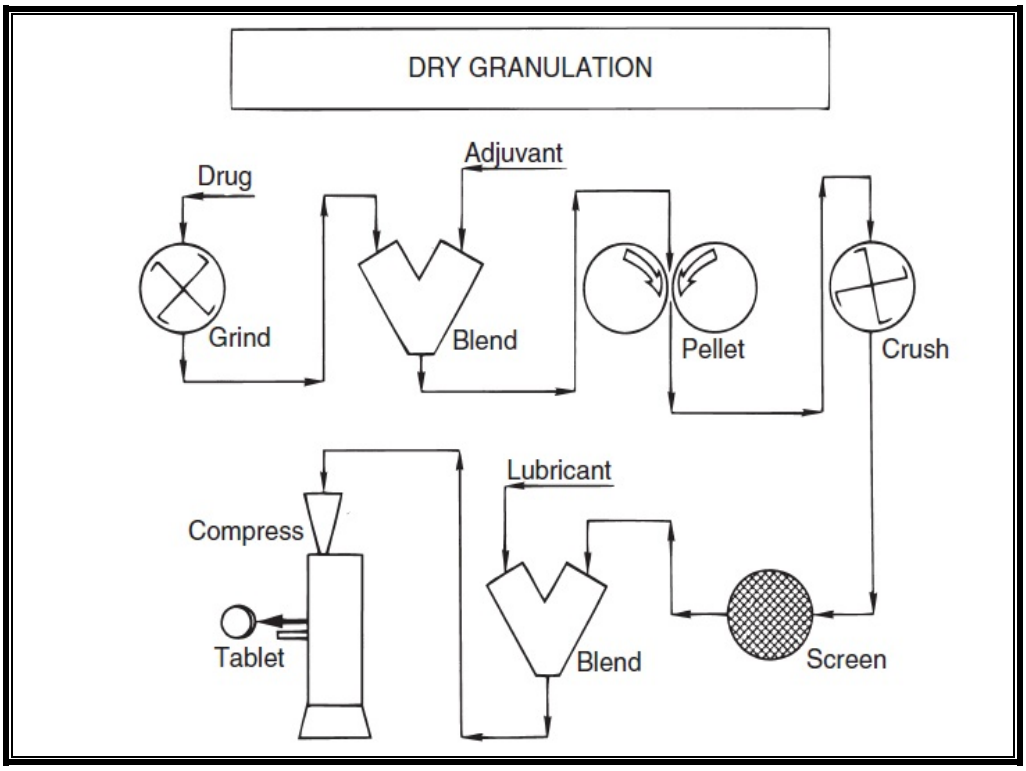


Figure 2.5: Dry Granulation Mechanism

In dry granulation process the powder mixture is compressed without the use of heat and solvent. The two basic procedures are to form a compact of material by compression and then to mill the compact to obtain granules.

Two methods are used for dry granulation. The more widely used method is slugging, where the powder is precompressed and the resulting tablets or slugs are milled to yield granules. The other method is to precompress the powder with pressure rolls using a machine such as Chilosonator.

Advantages:

The main advantages of dry granulation or slugging are that it uses less equipments and space. It eliminates the need for binder solution, heavy mixing equipment and the costly and time consuming drying step required for wet granulation. Slugging can be used for advantages in the following situations:

- For moisture sensitive material
- For heat sensitive material

- For improved disintegration since powder particles are not bonded together by a binder

Disadvantages:

• It requires a specialized heavy duty tablet press to form slug.

• It does not permit uniform colour distribution as can be achieved with wet granulation where the dye can be incorporated into binder liquid.

• The process tends to create more dust than wet granulation, increasing the potential contamination.

Steps in dry granulation:

1. Milling of drugs and excipients
2. Mixing of milled powders
3. Compression into large, hard tablets to make slug
4. Screening of slugs
5. Mixing with lubricant and disintegrating agent
6. Tablet compression

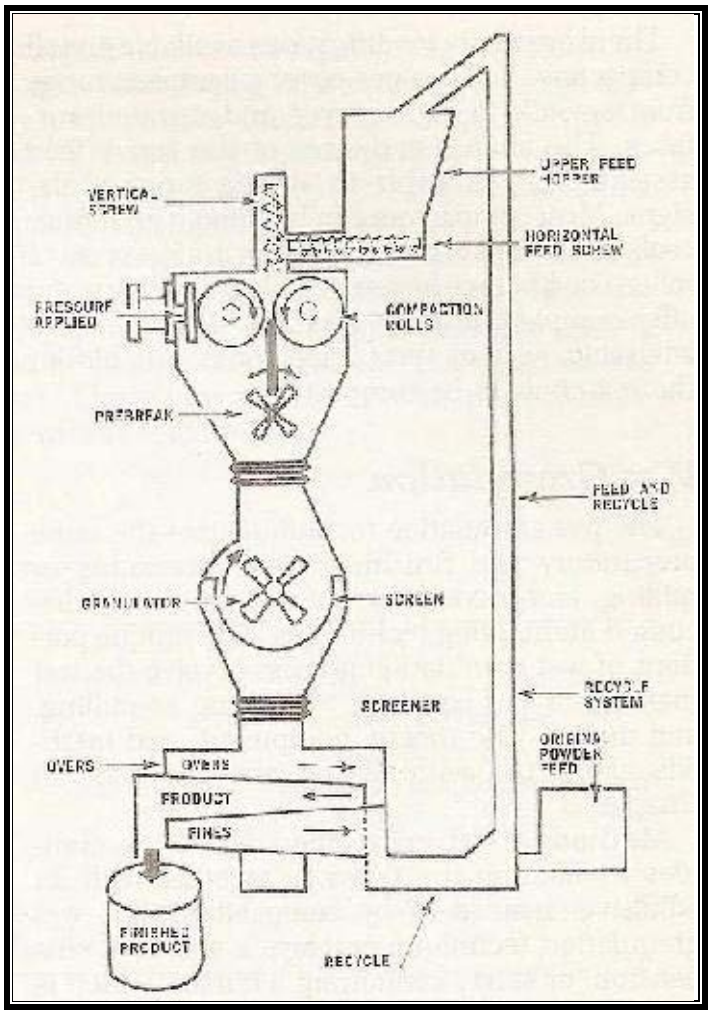


Figure 2.6: Schematic diagram of a Chilsonator Roller Compactor in a granulation production system

Two main dry granulation processes:

a. Slugging process

Granulation by slugging is the procedure of compacting dry powder of tablet plan with tablet press having pass on pit sufficiently substantial in breadth to fill rapidly. The exactness or state of slug is not very imperative. Just adequate weight to smaller the powder into uniform slugs ought to be utilized. When slugs are created they are decreased to fitting granule size for conclusive pressure by screening and processing.

b. Roller compaction

The compaction of powder by method for weight roll can likewise be proficient by a machine called Chilosonator. Dissimilar to tablet machine, the Chilosonator turns out a compacted mass in an unfaltering nonstop stream. The powder is sustained down between the rollers from the container which contains a winding twist drill to nourish the powder into the compaction zone. Like slugs, the totals are screened or processed for generation into granules.

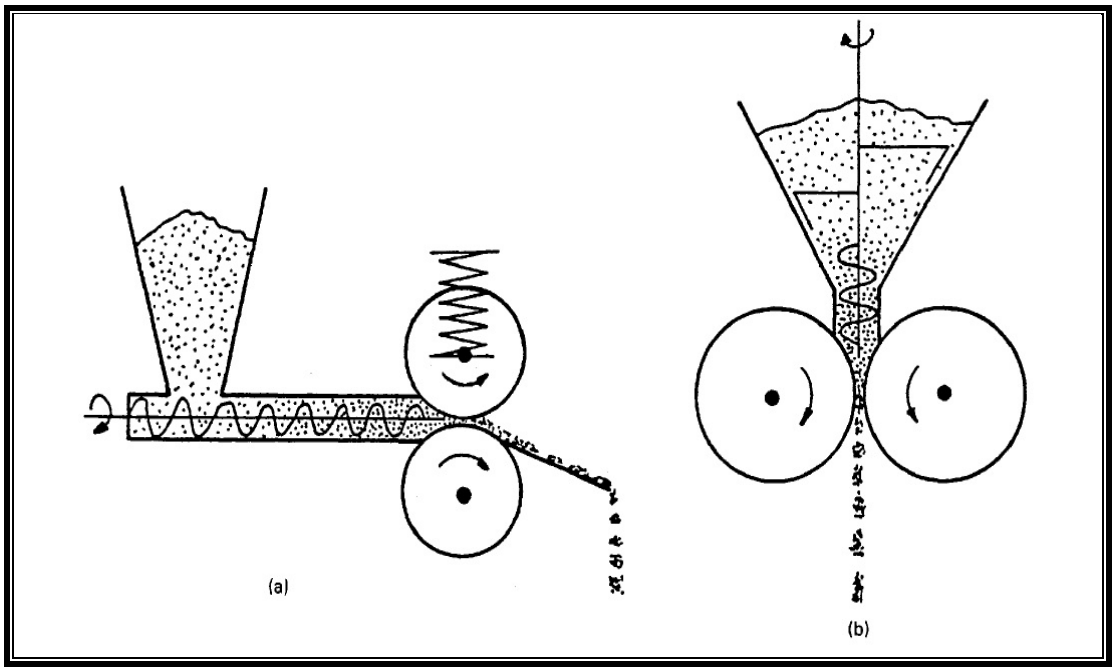


Figure 2.7: Roller Compacter: (a) Alexanderwerk and (b) Hutt types

Table No. 2.1: Typical Unit Operation involved in Wet Granulation, Dry Granulation and Direct Compression

Wet Granulation	Dry Granulation	Direct Compression
1. Milling and mixing of drugs and excipients	1. Milling and mixing of drugs and excipients	1. Milling and mixing of drugs and excipients
2. Preparation of binder Solution	2. Compression into slugs or roll compaction	2. Compression of tablet
3. Wet massing by addition of binder solution or granulating solvent	3. Milling and screening of slugs and compacted powder	-
4. Screening of wet mass	4. Mixing with lubricant and disintegrant	-
5. Drying of the wet Granules	5. Compression of tablet	-
6. Screening of dry Granules	-	-
7. Blending with lubricant and disintegrant to produce “running powder	-	-

3. Tablet Moulding[9]

In this technology, water-soluble ingredients are used so that tablet disintegrate and dissolve rapidly. The powder blend is moistened with a hydro alcoholic solvent and is moulded in to tablet using compression pressure lower than used in conventional tablets compression. The solvent is then removed by air-drying. Moulded tablets have a porous structure that enhances dissolution. Two problems commonly encountered are mechanical strength and poor taste masking characteristics. Using binding agents such as sucrose, acacia or poly vinyl pyrrolidone can increase the mechanical strength of the tablet. To overcome poor taste masking characteristic Van Scoik incorporated drug containing discrete particles, which were formed by spray congealing a molten

mixture of hydrogenated cottonseed oil, sodium bicarbonate, lecithin, polyethylene glycol and active ingredient into a lactose based tablet triturate form.

4. Mass-Extrusion[9]

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking.

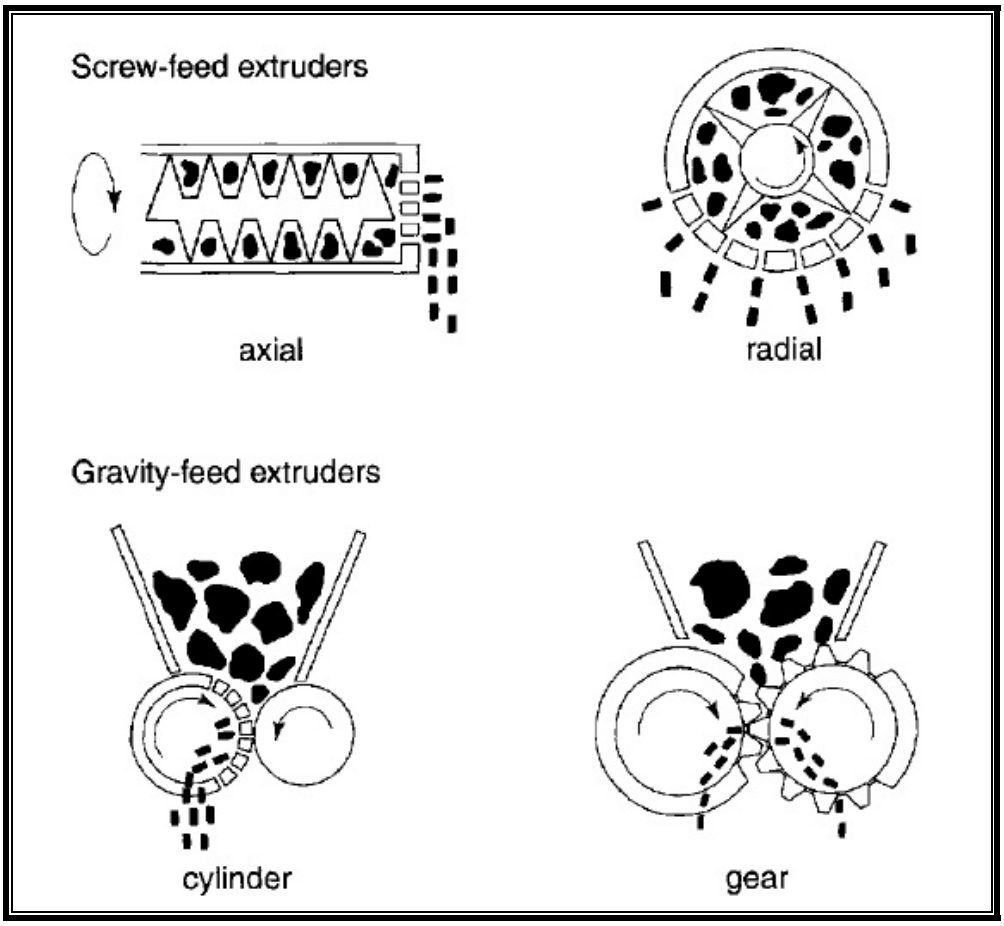


Figure 2.8: Various types of Extruder

5. Solid dispersions technique[9]

At the point when figuring such strong nebulous scatterings into prompt discharge strong measurement shapes for oral organization to an utilization domain, for example, the GI tract of a creature, for example, a human, it is regularly attractive to amplify the measure of scattering present in the dose structure. This minimizes the span of the strong dose structure required to accomplish the coveted dosage. Contingent upon the medication measurement, it is regularly sought that the strong undefined scattering include no less than 30 wt. %, ideally at any rate wt. %, and all the more ideally no less than 50 wt. % or a greater amount of the strong dose structure. Such high medication loadings of scattering in a strong dose structure minimize the measurement structure's size, making it simpler for the patient to swallow it and having a tendency to enhance quiet consistence.

2.4. Advancement Technique Used in the Preparation of Immediate Release Tablets[9]

1. Steam Granulation
2. Melt Granulation / Thermoplastic Granulation
3. Moisture Activated Dry Granulation (MADG)
4. Moist Granulation Technique (MGT)
5. Thermal Adhesion Granulation Process (TAGP)
6. Foam Granulation

2.5. List of Excipients Used in the Preparation of Immediate Release Tablets[10,11]

Excipients parity the properties of the actives in quick discharge measurement shapes. This requests a careful comprehension of the science of these excipients to anticipate cooperation with the actives. Deciding the expense of these fixings is another issue that should be tended to by formulators.

The part of excipients is essential in the detailing of quick discharge tablets. These dormant sustenance grade fixings, when consolidated in the plan, grant the sought organoleptic properties and item adequacy. Excipients are general and can be utilized for a wide scope of actives, with the exception of a few actives that require veiling operators.

Diluents or Fillers:

Fillers are added to plan to build the mass volume of the dynamic and subsequently the span of the tablet reasonable for taking care of. Great filler will have great similarity and stream properties, worthy taste, will be non-hygroscopic and ideally artificially inactive.

E.g.: mannitol, lactose, sorbitol, sucrose, and inositol, microcrystalline cellulose (Avicel®), Partial pregelatinised starch.

A material with a high holding capacity can be utilized as a cover to build the mechanical quality of the tablet. A fastener is generally a flexible material inclined to experience plastic (irreversible) distortion. Ordinarily, covers are polymeric materials, regularly with scattered strong state structures. A cover is frequently added to the granulation fluid amid wet granulation to enhance the cohesiveness and similarity of the powder particles, which helps development of agglomerates or granules. It is regularly acknowledged that fasteners included broke down structure, amid a granulation procedure, is more compelling than utilized as a part of dry powder structure amid direct pressure.

E.g.: Starch, gelatin, sucrose, glucose, dextrose and lactose are much of the time utilized as fasteners. Regular and engineered gums that have been utilized incorporate acacia, sodium alginate, ghatti gum, CMC, veegum and so forth. Starch glue in fluctuating fixation from 10-20% is utilized as a folio. HPMC, which is more dissolvable in chilly water when contrasted with boiling hot water, is additionally utilized as a part of extraordinary cases.

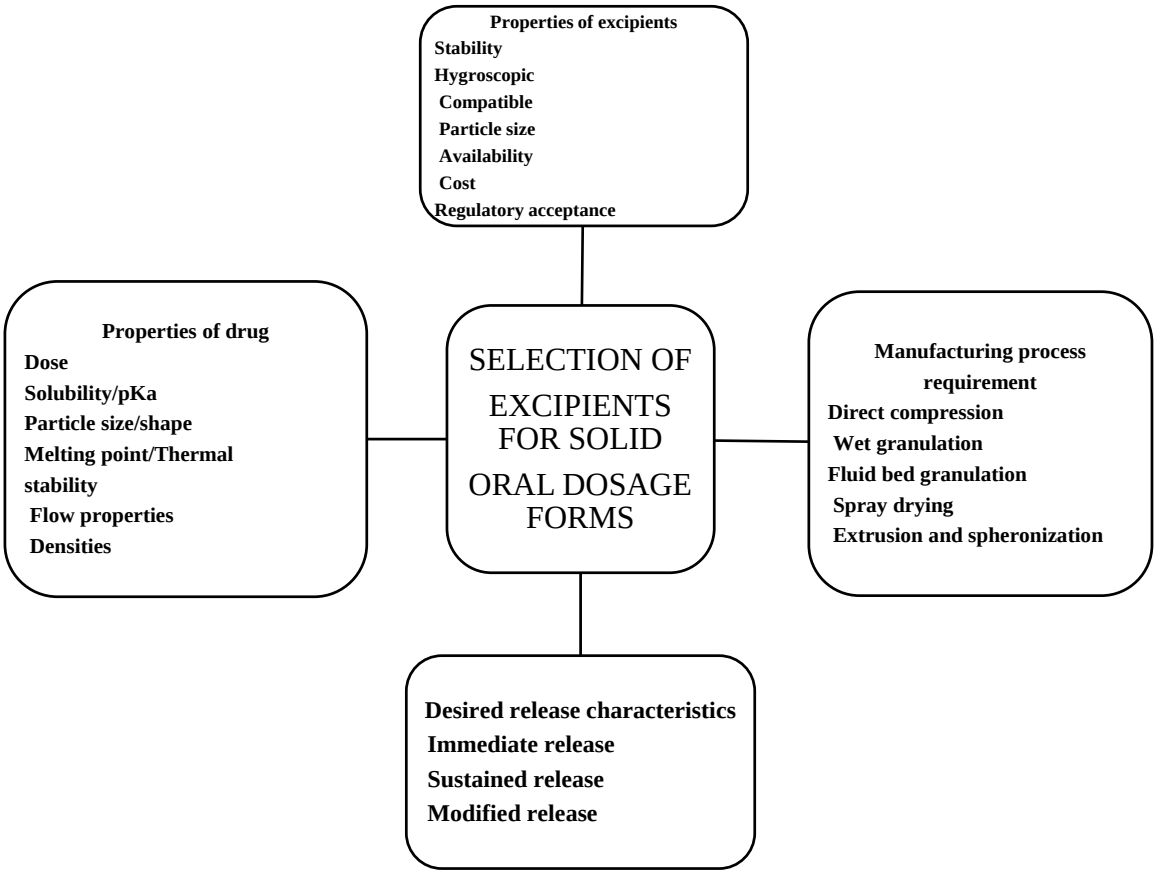


Fig. 2.9: Factors affect

Disintegrants:

As disintegrants sodium starch glycolate(SSG), sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, Crospovidone, polyvinyl polypyrrolidone, methyl cellulose, microcrystalline cellulose, powdered cellulose, lower alkyl-substituted hydroxypropyl cellulose, polacrilin potassium, starch, pregelatinized starch, sodium alginate, and blends thereof. The measure of disintegrant incorporated into the dose structure will rely on upon a few variables, including the properties of the scattering, the properties of the porosigen and the properties of the disintegrant chose. By and large, the disintegrant will involve from 1 wt. % to 25 wt. % of the measurement structure.

Porosigen:

A "porosigen" is a material that, when present in the definition containing the strong indistinct scattering, prompts a high porosity and high quality after pressure of the

mix into a tablet. What's more, favored porosigen are dissolvable in an acidic situation with fluid solvency regularly more noteworthy than 1 mg/mL at a pH not exactly around 5. Case of porosigen incorporate acacia, calcium carbonate, calcium sulfate, calcium sulfate dihydrate, compressible sugar, dibasic calcium phosphate, tribasic calcium phosphate, monobasic sodium phosphate, dibasic sodium phosphate, lactose, magnesium oxide, magnesium carbonate, silicon dioxide, magnesium aluminum silicate, maltodextrin, mannitol, methyl cellulose, microcrystalline cellulose, sorbitol, sucrose, xylitol and blends thereof. By and large, the porosigen will contain from 5 to 70 wt. %. To guarantee the tablet has adequate porosity to permit satisfactory wicking of water into the tablet to bring about fast tablet breaking down and/or quick arrival of medication, tablet porosity ought to be inside 0.15-0.25. In like manner, the disintegrant and porosigen ought to be chosen so that the prompt discharge dose structure has high strength and additionally the high porosity required to accomplish disintegration and/or drug release.

Surfactants:

One extremely valuable class of excipients is surfactants, ideally display from 0 to 10 wt. %. Appropriate surfactants incorporate unsaturated fat and alkyl sulfonates; business surfactants, for example, benzalkonium chloride, dioctyl sodium sulfosuccinate, polyoxyethylene sorbitan unsaturated fat esters, common surfactants, for example, sodium taurocholic corrosive, lecithin, and different phospholipids and mono-and diglycerides; and blends thereof. Such materials can beneficially be utilized to expand the rate of disintegration by, for instance, encouraging wetting, or generally build the rate of medication discharge from the measurement structure.

pH Modifiers:

Consideration of pH modifiers, for example, acids, bases, or cradles may likewise be advantageous in a measure of from 0 to 10 wt. %. Acidic pH modifiers (e.g., acids, for example, citrus extract or succinic corrosive) impede the disintegration of the pharmaceutical structure when the scattering polymer is anionic. On the other hand, essential pH modifiers (e.g., sodium acetic acid derivation or amines) improve the rate of disintegration of the same sorts of pharmaceutical organization.

Emulsifying Agents:

Emulsifying agents are vital excipients for detailing prompt discharge tablets they help in quick breaking down and medicate discharge. What's more, fusing emulsifying operators is helpful in settling the immiscible mixes and improving bioavailability. An extensive variety of emulsifiers is prescribed for quick tablet plan, including alkyl sulfates, propylene glycol esters, lecithin, sucrose esters and others. These operators can be joined in the scope of 0.05% to around 15% by weight of the last synthesis.

Glidant, antiadherent and lubricant (Antifrictional Agents):

Glidants are added to build the flowability of the powder mass, lessen interparticular grinding and enhance powder stream in the container shoe and pass on of the tableting machine. An antiadherent can be added to diminish adhering of the powder to the characteristics of the punches and the kick the bucket dividers amid compaction, and a grease is added to decline erosion amongst powder and bite the dust, encouraging discharge of the tablet from the pass on. The amount of ointment essentially shifts from 0.1 to 5%. The most regularly utilized glidants are colloidal silicon dioxide (Cabosil®, Cabot®) and asbestos free talc. They are utilized as a part of focus under 1%. Talc is likewise utilized and may fill the double need of oil/glidant.

Gas producing disintegrants

Gas creating disintegrants are utilized particularly where additional quick crumbling or promptly dissolvable definition is required. They have likewise been found of worth when poor breaking down qualities have opposed different techniques for development. Consideration ought to be taken amid tab letting, especially on dampness level. Creation is based upon the same standards as those utilized for foaming tablets, the most widely recognized being blends of citrus and tartaric acids in addition to carbonates or bicarbonates. In numerous occasions lower fixation can be utilized with gas creating disintegrants than are required by other crumbling specialists. Certain peroxides that discharge oxygen have been attempted, however they don't execute and in addition those discharging carbon dioxide.

Miscellaneous:

Wetting agents, Dissolution retardants, Dissolution enhancers, Buffers, Antioxidants, Chelating agents, Preservatives, Coloring agents.

2.6. Superdisintegrants[12,13,14]

A disintegrant is an excipient, which is added to a tablet or capsule blend to aid in the breakup of the compacted mass when it is put into a fluid environment. Disintegrating agent are substances routinely included in formulations for faster disintegration and immediate drug release. They promote moisture penetration and dispersion of the matrix of the dosage form in dissolution fluids. Super disintegrants improve disintegrant efficiency resulting in decreased used at a low level of disintegrants when compared to traditional disintegrants. Drug release from a solid dosage form can be enhanced by addition of suitable disintegrants. Super disintegrants are generally used at a low level in solid dosage form, typically 1-10% by weight relative to total weight of the dosage unit. The Superdisintegrants can be classified into two categories on the basis of their availability:

1. Natural Superdisintegrants:

These superdisintegrant-ting agents are natural in origin. The natural materials like gums and mucilage have been extensively used in the field of drug delivery for their easy availability, cost effectiveness, Eco friendliness, emollient and non-irritant nature, and non-toxicity, capable of multitude of chemical modifications, potentially degradable and compatible due to natural origin.

Advantages

- Cheaper,
- Abundantly available,
- Non-irritating,
- Nontoxic.

Table 2.2: List of Natural Superdisintedrants

Sr. No.	Natural Superdisintegrants	Source
1	Plantago Ovata Seed Mucilage	Seed of Plantago Ovata
2	Lapidium Sativum mucilage	Seed of Lapidium Sativum
3	Gum Karaya	Dried exudation of sterculia Urens tree.
4	Fanugreek Seed Mucilage	Seeds of fenugreek, TrigonellafoenumgraceumL
5	Guar gum	Seed of theguar plant, Cyamopsistetragonaloba
6	Cassia Fistula gum	Seed of Cassia fistula tree
7	Locust Bean Gum	Seed of Carob tree Ceretonia Siliqua
8	Hibiscus rosa-sinensis Linn Mucilage	Fresh Leaves of Hibiscus rosasinensis Linn

2. Synthetic Superdisintegrants:

A group of superdisintegrants including croscamellose sodium (Ac-Di-Sol) sodium starch glycolate (Primojeland Explotab) and crospovidone (Polyplasdone XL) alleviate most of these problems. Use of the superdisintegrants in fast dispersible tablet is possible as tablet shows optimum physical properties.

Advantages:

1. Effective in lower concentration
2. Less effect on compressibility and flowability
3. More effective intragranularly

Table 2.3: List of Synthetic Superdisintegrants

Superdisintegrants	Example	Mechanism Of Action	Special comment
Crosscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose®Solutab® Vivasol®L-HPC	Crosslinked cellulose	• Swells 4-8 foldsin < 10 seconds. • Swelling andwicking both.	• Swells in twodimensions . • Direct compressionor granulation • Starch free
Crosspovidone Crosspovidon M® Kollidon® Polyplasdone®	Crosslinked PVP	• Swells very littleand returns tooriginal size aftercompression butact by capillaryaction	• Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate Explotab® Primogel®	Crosslinked Starch	• Swells 7-12 folds in < 30 seconds	• Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF Satialgine®	Crosslinked alginic acid	• Rapid swelling in aqueous medium or wicking action	• Promote disintegration in both dry or wet granulation
Calcium silicate		• Wicking action	• Highly porous • 20-40%

Mechanism of action of disintegrants:

The tablet breaks to primary particles by one or more of the mechanisms listed below:

1. By porosity and capillary action

2. By swelling

3. Because of heat of wetting

4. Due to release of gases
5. Due to disintegrating particle/particle repulsive forces
6. Due to deformation
7. By enzymatic reaction

Method of incorporation of superdisintegrants:

The incorporation of superdisintegrants in the dosage forms are mainly of three types:-

1. **Intragranular or during granulation -** In this process the superdisintegrants are blend with other powders and granulation is carried out. Thus the superdisintegrants are incorporated within the granules.

2. **Extragranular or prior to compression -** In this process, the superdisintegrants are mixed with prepared granules before compression.

3. **Incorporation of superdisintegrants at intra and extra granulation steps-** In this process part of superdisintegrants are added to intragranular and a part to extragranules. This method usually produces better results and more complete disintegration than type I and type- II.

2.7. Coating Techniques[15,16,17]

Definition

Coating is a process by which an essentially dry, outer layer of coating material is applied to the surface of a dosage form in order to confer specific benefits that broadly ranges from facilitating product identification to modifying drug release from the dosage form. After making a good tablet, one must often coat it.

Basic principles involve in tablet coating

Tablet coating is the application of coating composition to moving bed of tablets with concurrent use of heated air to facilitate evaporation of solvent.

1. Solution in which influences the release pattern as little as possible and does not markedly change the appearance.
2. Modified release with specific requirement and release mechanism adapted to body function in the digestive tract.
3. Color coating which provides insulation.
4. To incorporate another drug or formula adjuvant in the coating to avoid chemical incompatibilities or to provide sequential drug release.
5. To improve the pharmaceutical elegance by use of special colors and contrasting printing.

Primary components involved in tablet coating

1) Tablet properties
2) Coating process
3) Coating equipments
4) Parameters of the coating process
5) Facility and ancillary equipments
6) Automation in coating processes.

Advantages of tablet coating

Tablet coatings must be stable and strong enough to survive the handling of the tablet, must not make tablets stick together during the coating process, and must follow the fine contours of embossed characters or logos on tablets.

Coatings can also facilitate printing on tablets, if required. Coatings are necessary for tablets that have an unpleasant taste, and a smoother finish makes large tablets easier to swallow.

Disadvantages of tablet coating

Disadvantages of sugar coating such as relatively high cost, long coating time and high bulk have led to the use of other coating materials. However the process of coating is tedious and time-consuming and it requires the expertise of highly skilled technician. The process is tedious and time-consuming and it requires the expertise of highly skilled technician.

Tablet Coating Types

Generally three methods are used for tablet coating

1. Sugar coating
2. Film coating
3. Enteric coating
   - Specialized coating

1. Compressed coating
2. Electrostatic coating
3. Dip coating
4. Vacuum film coating
   a) Fluid bed rotor Fluid Bed Bottom - spray Wurster
   b) Fluid bed top-spray
   c) Fluid Bed Bottom - spray Wurster
   - Recent trend in tablet coating

1. Electrostatic dry coating
2. Magnetically assisted impaction coating (MAIC)
3. Aqueous film coating technology
4. Super cell coating technology

2.7.1. Film Coating

If the following questions are answered concomitantly then one can go for film coating:

i) Is it necessary to mask objectionable taste, color and odor?

ii) Is it necessary to control drug release?

iii) What tablets size, shape, or color constrains must be placed on the developmental work?

Materials used in film coating

1. Film formers, which may be enteric or nonenteric
2. Solvents
3. Plasticizers
4. Colourants
5. Opaquant-Extenders
6. Miscellaneous coating solution components

I. Film formers

Ideal requirements of film coating materials are summarized below:

- Solubility in solvent of choice for coating preparation
- Solubility requirement for the intended use e.g. free water-solubility, slow water solubility or pH -dependent solubility
- Capacity to produce an elegant looking product
- High stability against heat, light, moisture, air and the substrate being coated
- No inherent colour, taste or odor
- High compatibility with other coating solution additives
- Nontoxic with no pharmacological activity
- High resistance to cracking
- Film former should not give bridging or filling of the debossed tablet
- Compatible to printing procedure

Commonly used film formers are as follow

1. Hydroxy Propyl Methyl Cellulose (HPMC)
2. Methyl Hydroxy Ethyl Cellulose (MHEC)
3. Ethyl Cellulose (EC)
4. Hydroxy Propyl Cellulose (HPC)

5. Povidon

6. Sodium carboxy methyl cellulose

7. Polyethylene glycols (PEG)

8. Acrylate polymers

II. Solvents

Solvents are used to dissolve or disperse the polymers and other additives and convey them to substrate surface.

Ideal requirement are summarized below

- Should be either dissolve/disperse polymer system
- Should easily disperse other additives into solvent system
- Small concentration of polymers (2-10%) should not in an extremely viscoussolution system creating processing problems
- Should be colorless, tasteless, odorless, inexpensive, inert, nontoxic andnonflammable.
- Rapid drying rate
- No environmental pollution

III. Plasticizers

IV. Colorants

V. Opaquant Extenders

VI. Miscellaneous coating solution component

Ideal properties of enteric coating material are summarized as below

- Resistance to gastric fluids
- Susceptible/permeable to intestinal fluid
- Compatibility with most coating solution components and the drug substrate
- Formation of continuous film
- Nontoxic, cheap and ease of application
- Ability to be readily printed3-5

Polymers used for enteric coating are as follow

1. Cellulose acetate phthalate (CAP)

2. Acrylate polymers

3. Hydroxy propyl methyl cellulose phthalate 4. Polyvinyl acetate phthalate

2.8. Hypertension

Definition

Hypertension (HTN) or high blood pressure, sometimes called arterial hypertension, is a chronic medical condition in which the blood pressure in the arteries is elevated. This requires the heart to work harder than normal to circulate blood through the blood vessels. Blood pressure is summarized by two measurements, systolic and diastolic, which depend on whether the heart muscle is contracting (systole) or relaxed between beats (diastole) and equate to a maximum and minimum pressure, respectively. Normal blood pressure at rest is within the range of 100-140mmHg systolic (top reading) and 60-90mmHg diastolic (bottom reading). High blood pressure is said to be present if it is persistently at or above 140/90 mmHg.

Table 2.4: Blood Pressure Levels for Adults

CATEGORY	**Systolic *(in mm Hg)**	**Diastolic * (in mm Hg)**
Optimal	less than 120	less than 80
Normal	less than 130	less than 85
High-normal	130–139	85–89
HYPERTENSION		
Stage 1	140–159	90–99
Stage 2	160–179	100–109
Stage 3	180 or higher	110 or higher
***If systolic and diastolic pressures fall into different categories, the patient's status is the higher category.**		

Classification of Antihypertensive drugs:

1. Diuretics: Thiazides: Hydrochlorthiazide, Chlorthalidone, Indapamide.High ceiling: Furosemide,etc. K+ Sparing : Spironolactone, Amiloride

2. ACE inhibitors: Captopril, Enalapril, Lisinopril, Ramipril,etc.

3. Angiotensin (AT1 receptor) blockers: Valsartan, Telmisartan, Candesartan, Irbesartan.

4. Calcium channel blockers: Diltiazem, Verapamil, Nifedipine, AHD Y, Felodipine, etc.

5. Beta Adrenergic blockers: Propanolol, Metoprolol, Atenolol, etc.

6. Beta + Alpha Adrenergic blockers: Labetalol, Carvedilol

7. Alpha Adrenergic blockers: Prazosin, Terazosin, Phenoxybenzamine, Phentolamine

8. Central sympatholytics: Clonidine, Methyldopa

9. Vasodilators: Arteriolar : Hydralazine , Minoxidil, Diazoxide Arteriolar+ venous: Sodium nitropusside

Recommended Combination for Hypertension

- **Preferred**
- ACE Inhibitor/diuretic
- ARB/diuretic
- ACE-Inhibitor/CCB
- ARB/CCB
- **Acceptable**
- Beta-blocker/diuretic
- CCB (dihydropyridine)/beta-blocker
- CCB/diuretic
- Renin inhibitor/diuretic
- Renin inhibitor/CCB
- Dihydopyridine CCB/non-dihydropyridine CCB

3. Literature Review

3.1. Literature Review of Dosage Form

Niemeijer MG26 et al[18] Combination treatment with antihypertensive specialists uses diverse instruments of activity and might be in charge of a more compelling diminishing in circulatory strain. The twofold visually impaired American Combination of AHD in Controlling High Blood Pressure study (2008) appeared in 1,940 patients that following eight weeks of treatment the BP objectives were most every now and again accomplished in the 'mix treatment bunch', with 56.3% (54.1–58.5%) and 54.0% (51.8–56.2%) of patients achieving sufficient pulse of <140/90 mmHg with olmesartan/amlodipine 20/10 and 40/10 individually. Blend treatment was for the most part very much endured. The most widely recognized reaction was oedema [olmesartan 20 mg 9.9% (8.6–11.3%), amlodipine 10 mg 36.8% (34.7–39.0%), fake treatment 12.3% (10.9–13.8%)]. The recurrence of oedema was lower in the gatherings consolidating amlodipine 10 mg with olmesartan 10 mg (26.5%, 24.5–28.5%), 20 mg (25.6%, 23.7–27.6%) or 40 mg (23.5%, 21.6–25.4%). In 2009 three twofold visually impaired controlled European studies including 500–1,000 patients each and performed autonomously of each other have affirmed the above study, and have shown comparable viability wellbeing impacts from the mix of olmesartan medoxomil with amlodipine, especially for patients not accomplishing satisfactory circulatory strain control with olmesartan monotherapy. Mixes of olmesartan and amlodipine were essentially more successful at decreasing circulatory strain and acknowledging rule pulse objectives in patients with gentle to serious hypertension than monotherapy (with a fake treatment part). Blend treatment is all around endured and is connected with a lower frequency of reactions, for example, oedema, contrasted with monotherapy with high amlodipine measurements (10 mg).

Chrysant SGet al[19] concentrated on that Hypertension is especially pervasive in patients matured ≥ 65 years, those with a body mass record ≥ 30 kgm-2, Blacks and those with sort II diabetes. He was accounted for prespecified auxiliary examination of the adequacy of amlodipine (10mgday-1), olmesartan medoxomil (40mgday-1), a mix of the two and fake treatment in these subgroups. Patients were randomized to

treatment for 8 weeks. The essential viability endpoint was the change from standard in mean situated diastolic pulse (DBP). Optional viability endpoints incorporated the change from benchmark in mean situated systolic BP (SBP), extents of patients accomplishing BP objective (<140/90mmHg or <130/80mmHg in patients with diabetes), and the number and rate of patients accomplishing a scope of BP targets. Wellbeing and bearableness of amlodipine 5 and 10 mg, olmesartan medoxomil 10, 20 and 40 mg, and every single conceivable mix of the two were additionally evaluated. For each prespecified subgroup, every dynamic treatment brought about noteworthy BP diminishments from benchmark (P<0.05). The antihypertensive impact of the blend of amlodipine + olmesartan medoxomil was by and large more noteworthy than the constituent amlodipine or olmesartan medoxomil monotherapies, paying little mind to subgroup. When all is said in done, more patients getting blend treatment accomplished BP objective than those treated with monotherapies. The wellbeing and bearableness of mixes were like monotherapies over the subgroups. These outcomes propose that the blend of amlodipine + olmesartan medoxomil gives a protected and powerful choice for the treatment of hypertension in testing tolerant populaces.

Gradman AH et al[20]studied that at least 75% of patients will require combination therapy to achieve contemporary BP targets, and increasing emphasis is being placed on the practical tasks involved in consistently achieving and maintaining goal BP in clinical practice. It is within this context that the American Society of Hypertension presents this Position Paper on Combination Therapy for Hypertension. It will address the scientific basis of combination therapy, present the pharmacologic rationale for choosing specific drug combinations, and review patient selection criteria for initial and secondary use. The advantages and disadvantages of single pill (fixed) drug combinations, and the implications of recent clinical trials involving specific combination strategies will also be discussed.

Bramlage Peter et al[21] studied to assess the efficacy and tolerability of a fixed-dose combination of olmesartan and amlodipine in an unselected population of patients in primary care and to compare the results with recent randomized controlled trial evidence. A multicenter, non-interventional, non-controlled observational study

with 8241 hypertensive patients seen by 2187 physicians in daily practice. Blood pressure (BP) reduction, comorbid disease, pharmacotherapy, and tolerability were documented over a 12–18-week observational period. Patients had a mean age of 62.8 ± 11.8 years (48.1% female), and 74.8% had at least one comorbid risk factor or condition. In total, 51.3% received olmesartan-amlodipine 20/5 mg, 30.6% received 40/5 mg, and 17.9% received 40/10 mg at baseline, mostly because of lack of efficacy on prior antihypertensive therapy (73.8%). BP at baseline was 161.8 ± 16.6/93.6 ± 10.2 mmHg (39.8% had Grade 2 hypertension), and the observed BP reduction was −29.0 ± 17.1/−13.5 ± 10.9 mmHg ($P < 0.0001$), with a significant correlation between BP at baseline and BP reduction (Spearman's Rho −0.811 for systolic BP and −0.759 for diastolic BP). BP reduction appeared to be dependent on dose and prior antihypertensive therapy, but not on age, gender, body mass index, duration of hypertension, or the presence of diabetes. At the final visit, 69.4% (4.3% at baseline) were controlled (<140/90 mmHg). Adverse drug reactions were observed in 2.76% of the study population; 94.25% of these adverse drug reactions were judged as non serious events, and 31.5% of all adverse drug reactions reported were peripheral edema. The fixed-dose olmesartan-amlodipine combination was effective and well tolerated in an unselected population of patients in primary care practice. These results confirm prior randomized controlled trial evidence.

Volpe Massimo et al[22] studied that Hypertension is a developing worldwide wellbeing issue, and is anticipated to influence 1.56 billion individuals by 2025. Treatment remains imperfect, with control of circulatory strain accomplished in just 20%–35% of patients, and the larger part requiring two or more antihypertensive medications to accomplish suggested pulse objectives. To enhance circulatory strain control, the European hypertension rules suggest that angiotensin II receptor blockers (ARBs) or angiotensin-changing over protein inhibitors (ACEIs) are consolidated with calcium channel blockers (CCBs) and/or thiazide diuretics. The justification for this procedure is based, to a limited extent, on their distinctive consequences for the renin-angiotensin framework, which enhances antihypertensive viability. Information from an extensive number of trials backing the viability of ACEIs or ARBs in mix with CCBs and/or hydrochlorothiazide (HCTZ). Consolidating two diverse classes of antihypertensive medications additively affects bringing down of pulse, and does not

increment unfriendly occasions, with the ARBs demonstrating an averageness advantage over the ACEIs. Among the diverse ARBs, olmesartan medoxomil is accessible as a double altered measurement blend with either amlodipine or HCTZ, and the expanded circulatory strain bringing down viability of these two mixes is demonstrated. Triple treatment is required in 15%–20% of treated uncontrolled hypertensive patients, with a renin-angiotensin framework blocker, CCB, and thiazide diuretic thought to be a balanced mix as per the European rules. Olmesartan, amlodipine, and HCTZ are accessible as a triple settled measurement blend, and noteworthy circulatory strain diminishments have been seen with this regimen contrasted and the conceivable double mixes. The accessibility of these settled dosage mixes ought to prompt change in circulatory strain control and help consistence with long haul treatment, enhancing the administration of this interminable condition.

3.2. Literature Review of Drug

Raj BS et al[23] studied that Amlodipine is a sparingly solvent orally managed drug and the rate of ingestion is frequently controlled by the rate of disintegration. The rate of disintegration will increment by fusing the medication in a quick dissolving measurements structure. An endeavor will be made to grow quickly deteriorating oral tablets of Amlodipine Besylate by direct pressure strategy. In this concentrate, Fast Dissolving Tablet (FDT) was readied utilizing direct pressure strategy utilizing Crospovidone and Sodium starch glycolate as the super disintegrants. Amongst all details, definition arranged by a mix of both Crospovidone and Sodium starch glycolate demonstrated slightest breaking down time, and quicker disintegration of 87%. Blend of super disintegrants were observed to be ideal to plan quick dissolving tablets of Amlodipine Besylate.

Shelke PV et al considered that Fast dissolving oral movies (FDOFs) are the most exceptional type of oral strong measurements structure because of more adaptability and solace. It enhance the viability of APIs by dissolving inside moment in oral cavity after the contact with less spit when contrasted with quick dissolving tablets, without biting and no need of water for organization. Quick dissolving film of Amlodipine

Besylate was readied utilizing sodium alginate as film shaping polymer. To diminish the deterioration time of plans sodium starch glycolate was utilized as breaking down operator. An entire 32 factorial configuration was connected utilizing centralization of polymer and disintegrant as autonomous variable and deterioration time and % combined medication discharge as reliant variable. Reaction surface bends were plotted. Quick dissolving movies were readied utilizing sodium alginate as film framing polymer and sodium starch glycolate as crumbling specialist. The movies were assessed for different properties, for example, thickness, drug content and so forth. The outcome demonstrated that all the movies have a smooth surface and great collapsing perseverance. Drug substance of all the movies was between 4.6 to 5.01mg. All the nine definition was demonstrating around 70-85% medication discharge after 6 min. The outcome demonstrates that crumbling of movies introduced in around 30 sec and finishes in 142-197 sec.

Raval Chirag et al[24] studied that Olmesartan Medoxomil (OLM) is an angiotensin II receptor blocker antihypertensive operator. It is a profoundly lipophilic (log p (octanol/water) 5.55), inadequately water dissolvable medication with total bioavailability of 26%. The goals of the present examination was to build up a self-small scale emulsifying drug conveyance framework (SMEDDS) to upgrade the dissolvability and that may improve the oral bioavailability of inadequately water solvent OLM. The solvency of OLM was resolved in different vehicles like oils, surfactants and co-surfactants. Arranged SMEDDS was checked for stage partition, thickness, bead size, zeta potential and in vitro disintegration. The streamlined SMEDDS plan contained Tween 20 (45%), Propylene glycol (45%) and Capmul MCM 10 (10%), 20 mg of OLM demonstrating drug discharge (99.35%), bead size (36.4 nm), polydispersity (0.186), consistency (0. 8872 cP) and vast weakening capacity. In vitro drug arrival of the upgraded fluid SMEDDS definitions was profoundly huge ($p < 0.05$) when contrasted with advertised routine tablet and unadulterated medication arrangement. The advanced fluid SMEDDS was further utilized for the readiness of Solid SMEDDS (S-SMEDDS) details by utilizing adsorption transporters. The advanced plan of OLM-stacked S-SMEDDS showed complete in vitro drug discharge in 60 min as thought about immaculate medication arrangement The outcome affirmed that the potential utilization of SMEDDS to

enhance disintegration and oral bioavailability of ineffectively water-dissolvable OLM.

Sasidhar et al[25] studied that to mask metallic taste and enhanced solubility and dissolution rate of poorly soluble OLM by formulating it as inclusion complexes with β-cyclodextrins (β-CDs) as complexing agent in 1:1 molar ratio. The drug – CDs complexes were prepared by physical mixing and co-evaporation methods. The complex formation with in solid state was confirmed by Fourier transform infrared spectroscopy, x-ray diffractometry, differential scanning colorimetry and by scanning electron microscope analysis. From the prepared inclusion complexes, orodispersible tablets (ODTs) were formulated by using various superdisintegrants like sodium starch glycolate (SSG) and crospovidone in various concentrations (5-15%).ODTs containing SSG (15%) as super-disintegrant showed fastest disintegration and in vitro drug release. In conclusion, the present investigation demonstrates that the combination of inclusion complexation and using of superdisintegrants was a promising approach in the preparation of tastes masked ODTs of OLM. The inclusion complex prepared by kneading method released the drug more rapid than the complexes prepared by physical mixing and pure drug alone. It was found that the tablet formulation with 15 % SSG showed the rapid drug release when compared to pure drug and inclusion complex prepared by physical mixing. inclusion complex prepared by the kneading method released the drug more rapid than the pure drug and complexes prepared by physical mixture and the metallic taste of the OLM was effectively masked by inclusion complexation with CDs. The orodispersible tablets of OLM prepared with SSG as superdisintegrant showed rapid drug release when compared to pure drug and other tablet formulations.

3.3. Literature Review of Excipient

Rath et al[26] studied that Telmisartan is an angiotensin II (AT1) receptor adversary utilized as a part of the treatment of hypertension. The medication is for all intents and purposes insoluble in water and insoluble in the pH range 3-9. The primary point of this work was to discover the impact of sodium starch glycolate and β – cyclodextrin

on the disintegration profile of prompt discharge telmisartan tablets and to streamline their qualities by a 22 Full factorial outline. Different excipients utilized as a part of the study are microcrystalline cellulose (Avicel PH-101) and magnesium stearate. Both sodium starch glycolate and β – cyclodextrin had commitment towards the prompt discharge yet the impact of sodium starch glycolate is more claimed from reaction surface plot and in addition from the form plot. The advanced measure of sodium starch glycolate and β – cyclodextrin were observed to be 55.714 mg and 30 mg separately for 70 % drug discharge at 30 minutes. Instrument of medication discharge was observed to be through dispersion and also polymer unwinding as uncovered from the incline of the Korsmeyer Peppas model.

Galge Deepak et al[27] studied that Irbesartan blocks the vasoconstrictor and aldosterone secreting effect of angiotensin II by selectively binding to the AT1 angiotensin II receptor. ACE inhibitor is used in treatment of hypertension. Irbesartan tablet have been formulated by wet granulating method. Effect of various filler and disintegrants also explored. Microcrystalline cellulose, colloidal silicone dioxide, croscarmelose sodium were used in wet granulation. Formulation containing irbesartan with croscarmelose sodium gives highest cumulative percent release (99.57%) in 20 min. All tablets released almost 85 % of drug within 20 min.

Prasad H M et al[28] studied that building up a Glimepiride prompt discharge tablet definition for the compelling treatment of Type-2 Diabetes mellitus (or) Non-Insulin-Dependent Diabetes Mellitus (or) grown-up onset diabetes. Glimepiride is a sulfonylurea antidiabetic drug. Glimepiride goes about as an insulin secretagogue. To furnish the patients with the most advantageous method of organization, there was a need to create prompt discharge dose structure, especially one that crumbles quickly and scatters and aides in upgrading the Bioavailability of the medication. Glimepiride quick discharge tablets were detailed by utilizing wet granulation technique and povidone k 30, starch as fasteners, croscarmellose sodium, Sodium Starch Glycolate, Crospovidone as disintegrants, Lactose monohydrate as Diluent and Magnesium stearate as Lubricant. The tablets were assessed for Pre pressure and Post pressure Parameters subsequent to leading Preformulation Studies. Every one of the parameters were inside as far as possible and the medication crumbling time was less

and the In vitro disintegration ponders demonstrated that the medication discharge was quick in Formulation containing Sodium Starch Glycolate as Super disintegrant and Povidone k 30 as Binder when contrasted with every other Formulation.

3.4. Literature Review of Patents

Yada et al[29] examined that a pharmaceutical tablet containing olmesartan medoxomil and amlodipine besylate, Which has enhanced dissolvability. The piece contains (An) olmesartan medoxomil and (B) amlodipine besylate as dynamic fixings and (C) a calcium containing added substance. A technique for treating or averting hypertension by managing the pharmaceutical tablet to a patient.

Drugs Which consolidate olmesartan medoxomil and amlodipine (flyer of International Patent Publication WO 2004/067003) and drugs Which join olmesartan medoxomil and hydrochlorothiaZide (leaflet of International Patent Publication WO 2002/04 1 890) are knoWn in the earlier workmanship, however there is no knoWn strong measurements shape, for example, that of the present creation containing olmesartan medoxomil and amlodipine having enhanced disintegration properties as an aftereffect of the further incorporation of excipients containing calcium. Besides, there is no knoWn strong measurement frame, for example, that of the present creation containing olmesartan medoxomil, amlodipine and hydrochlorothiaZide having enhanced disintegration properties as a consequence of the further consideration of excipients containing calcium.

Eriksson et al[6] studied that a solid oral immediate release dosage form of a pharmaceutically active compound, N-[(1,2,3,4-tetrahydro-5-methyl-8-(4-methylpiperaZin-1yl)-2-naphthyl]-4-morpholinobenZamide, in the form of the free base or pharmaceutically acceptable salts thereof. The invention further relates to processes for preparing said dosage form, the use of said dosage form and a method of prevention and/or treatment of CNS disorders and related medical disturbances using said dosage form.

Dedhiya et al[30] studied thatthe present invention provides an immediate release composition for the low solubility drug, lercanidipine. The immediate release composition of the present invention comprises a core; a first layer, comprising lercanidipine, a surfactant and a binder, and optionally, a second layer comprising a film coating. Solid oral drug compositions or preparations have various release profiles such as an immediate release profile as referenced by FDA guidelines ("Dissolution Testing of Immediate Release Solid Oral Dosage Forms", issued 8/1997, Section IV-A) or an extended release profile as referenced by FDA Guidelines ("Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations", Food and Drug Administration, CDER, September 1997, Page 17). For example, in the dissolution testing guideline for immediate release profiles, materials Which dissolve at least 80% in the first 60 minutes, or in the first 30 minutes, an aqueous medium qualify as immediate release profiles.

Various components having different release characteristics may be employed to yield compositions having a multiphase release profile, such as a portion of drug releasing immediately, followed by an extended release, to attain more specific therapeutic objectives.

Thosar et al[7] concentrated on that the powerful organization of eplerenone to a subject has been convoluted by the compound's low solvency and low compressibility and in addition by its other physical and concoction properties. Pharmaceutical arrangements containing micronized eplerenone and a pharmaceutically adequate transporter material, nonetheless, have been found that can successfully convey a remedially favored measure of the compound to the subject. What's more, one of a kind blends of transporter material With the micronized eplerenone have been found that give still better solubilization qualities. These mixes of dynamic compound and transporter material have been found to have enhanced bioavailability, substance dependability, physical strength, disintegration profiles, breaking down times, security, and additionally other enhanced pharmacokinetic, synthetic and/or physical properties. The present creation contains these pharmaceutical pieces, unit dose shapes based consequently, and strategies for the readiness and utilization of both.

Bauer et al[31] studied that a stable solid dosage form comprising olmesaitan medoxomil and amlodipine or a pharmacologi cally acceptable salt thereof. In particular, it relates to solid dosage forms free from reducing sugars. The stable solid dosage form may optionally further comprise hydrochlorothiazide or a pharmacologically acceptable salt thereof.

A solid dosage form comprising olmesartan medoxomil and amlodipine or a pharmacologically acceptable salt thereof with improved stability of the active ingredients and reduced weight. In accordance With the present invention, problems associated With the preparation of a solid dosage form com prising olmesartan medoxomil and amlodipine or a pharmacologically acceptable salt thereof can best be handled by means of the preparation of formulations that are substantially free of reducing sugar in the formulation.

4. Experimental Work

4.1. Material used in present work

Table 4.1. : List of Material used

Sr.	Materials	Suppliers
1	Microcrystalline cellulose (Comprecell 101)	DFE Pharm Pvt Ltd
2	Microcrystalline cellulose (Comprecell 102)	DFE Pharm Pvt Ltd
3	Microcrystalline cellulose (Comprecell 112)	DFE Pharm Pvt Ltd
4	Cross carmellose Sodium (Ac-di-sol)	Signetchemical corporation pvt ltd
5	Mannitol (Pearlitol SD 200)	Roquetteriddhi siddhi pvt. ltd
6	Mannitol (Pearlitol 25C)	Roquetteriddhi siddhi pvt. ltd
7	Low substituted hydroxyl propyl cellulose LH 11	ShinEtstupolymer india pvt.ltd
8	Corn Starch	GPC
9	Sodium Lauryl sulfate (SLS)	BASF india ltd
10	Vitamin E TPGS	BASF india ltd
11	Poloxamer 407	BASF india ltd
12	Lactose monohydrate (Pharmatose 200M)	DFE Pharm Pvt Ltd
13	Lactose Anhydrous (DCL –21)	DFE Pharm Pvt Ltd
14	Pregelatinised Starch (Lycatab PGS)	Roquetteriddhi siddhi pvt. ltd
15	Pregelatinised Starch 1500 LM	Colorconasia pvt ltd
16	Stearic Acid 95	Taurus chemicals pvt ltd
17	Colloidal Anhydrous Silica (Aerosil 200)	NovaChem drugs pvt ltd
18	Sodium Steryl Fumarate	Signetchemical corporation pvt ltd
19	Magnesium Stearate	Dr. Paul lohmann
20	OPADRY® (HPMC Based)	Colorconasia pvt ltd

4.2. Equipment used in present work

Table 4.2: List of Instruments Used

Sr.	Equipment	Manufacturer
1	Electronic Weighing Balance	Mettler Toledo.
2	Electromagnetic sieve shaker	Electrolab India Ltd
3	Tap density apparatus	Electrolab India Ltd
4	8 station compression machine	CADMACH
5	16 station compression machine	CADMACH
6	Tray Dryer	Mevish Pharmaceutical Equipment Ltd.
7	Rapid Mixture Granulator	Saral Engg. Company
8	Cage Blender	Bectochem Engg. Pvt. Ltd.
9	Fluidized Bed Dryer	Alliance Engg. Company Ltd
10	Halogen Moisture Analyser	Mettler Toledo.
11	Milling (Comill)	GANSON & QUADRO Engg.
12	Oscillating Granulator	CADMACH
13	Tablet Hardness tester	Dr. Schleuniger
14	Vernier calipers	Mitutoyo, Aurora, Usa
15	Friability apparatus	Electrolab India Ltd.
16	Disintegrating Apparatus	Electrolab India Ltd.
17	Motor	Remi Engg. Ltd.
18	Coating Machine	Ganson India Ltd.
19	UV spectrophotometer	Shimadzu 1800-Pc
20	Dissolution Appratus (Autosampler)	Electrolab India Ltd
21	HPLC system	Agilent Technology Ltd.

4.3.Methodology

4.3.1. Preparation of Buffer solutions

4.3.1.1. Preparation of 0.1N Hydrochloric acid: 8.5 ml of concentrated hydrochloric acid was diluted with distilled water to produce 1000 ml.

4.3.1.2. Preparation of 0.2 M Potassium Dihydrogen Phosphate: Dissolve 27.218 g of potassium dihydrogen phosphate in water and dilute with water to 1000 ml.

4.3.1.3. Preparation of 0.2 M sodium hydroxide solution: 8g of sodium hydroxide was dissolved in water and diluted with water to 1000ml.

4.3.1.4. Preparation of phosphate buffer pH 6.8: Place 50.0 ml of 0.2 M potassium dihydrogen phosphate in a 200-ml volumetric flask, add 22.4 ml of 0.2 M sodium hydroxide and then add water to volume.

4.3.2. Determination of absorbance maxima of AHD X and AHD Y

A solution of AHD Y and AHD X containing the concentration 10 µg/ml was prepared by using phosphate buffer pH 6.8 respectively, UV spectrum was taken using Shimadzu 1800 – Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400nm.

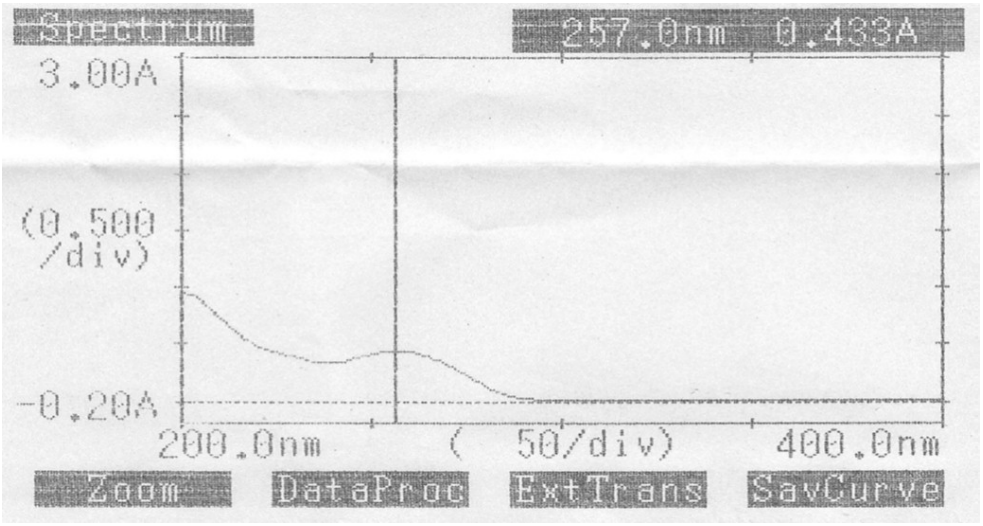


Figure 4.1: UV Spectrum of AHD X in pH 6.8 phosphate buffer

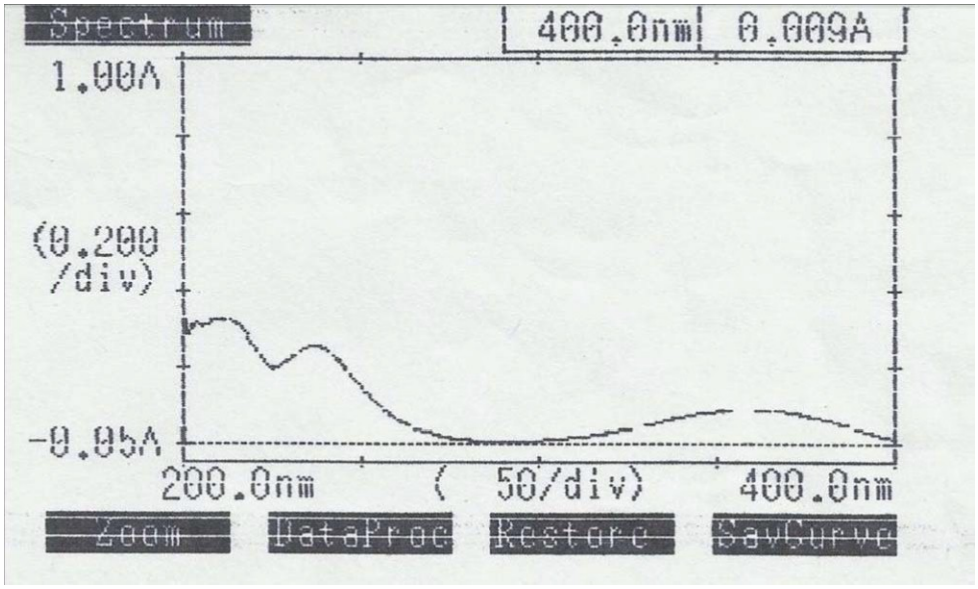


Figure 4.2: UV Spectrum of AHD Y in pH 6.8 phosphate buffer

For the determination of Absorbance Maxima, API were scanned in the wavelength range of 200-400 nm by UV-visible spectrophotometer. In above UV spectra, shows that λmax of AHD X and AHD Y in Phosphate buffer pH 6.8 was found to be 257.0 & 239.0 nm respectively.

4.3.2.1. Preparation of Standard Calibration curve of AHD X

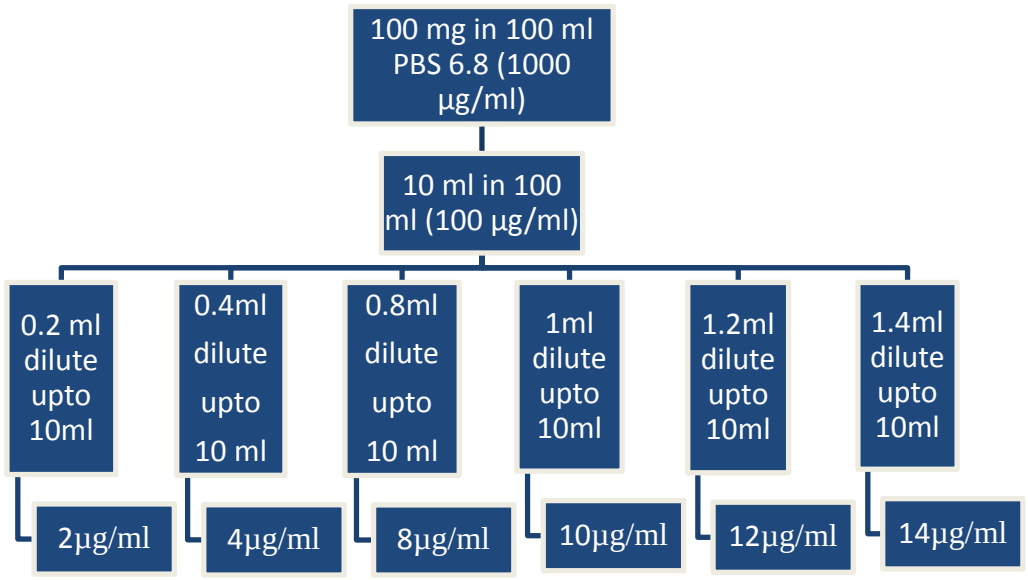


Figure: 4.3 Dilution Scheme for Calibration Curve of AHD X in pH 6.8 Buffer

100 mg accurately weight AHD X dissolve in 20 ml acetonitrile and make up to 100 ml in volumetric flask by using phosphate buffer pH 6.8. From this prepared solution, 10 mlsolution was taken and make up to 100 ml in volumetric flask by using phosphate buffer pH 6.8. The prepared solution is 100 µg/ml. From 100 µg/ml solution pipette out 0.2, 0.4, 0.8, 1.0, 1.2 and 1.4ml in 10 ml volumetric flask & Diluted up to 10 ml with pH 6.8 buffer. So prepared solution was 2, 4, 8, 10, 12 and 14 µg/ml respectively. The absorbance of the solutions was measured spectrophotometrically at 257 nm.

Table: 4.3 Standard calibration curve of AHD X in Phosphate buffer pH 6.8 at 257nm

Sr. No.	Concentration (µg/ml)	Absorbance			Average Absorbance
		1	2	3	
1	0	0	0	0	0
2	2	0.0807	0.0859	0.0932	0.0866
3	4	0.1740	0.1660	0.1790	0.1730
4	6	0.2532	0.2658	0.2604	0.2598
5	8	0.3421	0.3489	0.3467	0.3459
6	10	0.4280	0.4350	0.4360	0.4330
7	12	0.5205	0.5145	0.5235	0.5195
8	14	0.6180	0.6098	0.6208	0.6162

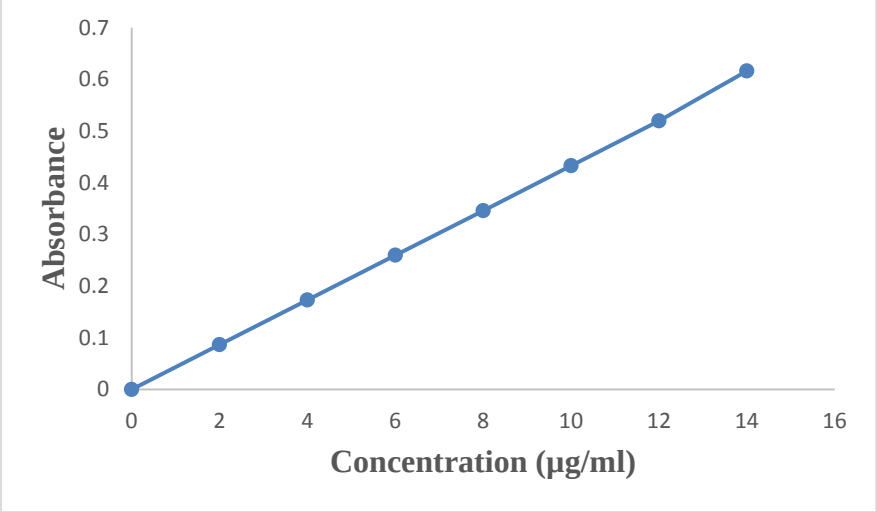


Figure 4.4: Standard Calibration curve of AHD X in 6.8 phosphate buffer solution

Standard calibration curve of AHD X in 6.8 phosphate buffer solution was prepared by plotting graph of absorbance vs. concentration. The absorbance of the sample solution was measured at λ_{max} 257 nm (Figure 4.4). A linear plot was obtained as shown in figure 4.4 that gives following linear equation, y = 0.0437x + 0.0017 and R^2value was 0.9998.

4.3.2.2. Preparation of Standard Calibration curve of AHD Y

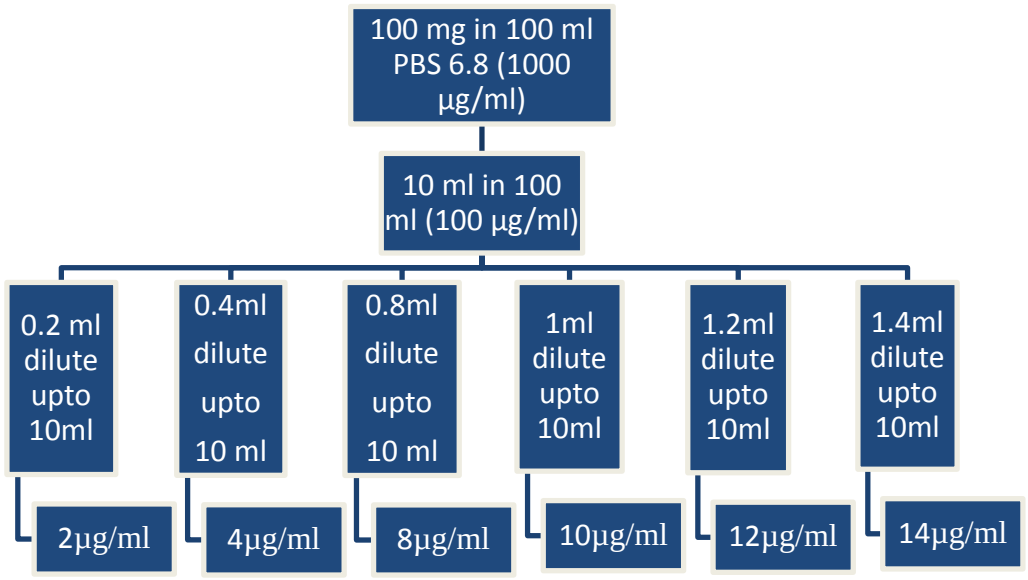


Figure 4.5: Dilution Scheme for Calibration Curve of AHD Y in pH 6.8 buffer

100 mg accurately weight AHD Y dissolve in 20 ml methanol and make up to 100 ml in volumetric flask by using phosphate buffer pH 6.8. From this prepared solution, 10 ml solution was taken and make up to 100 ml in volumetric flask by using phosphate buffer pH 6.8. The prepared solution is 100 µg/ml. From 100 µg/ml solution pippet out 0.2, 0.4, 0.8, 1.0, 1.2 and 1.4ml in 10 ml volumetric flask & Diluted up to 10 ml with pH 6.8 buffer. So prepared solution was 2, 4, 8, 10, 12 and 14 µg/ml respectively. The absorbance of the solutions was measured spectrophotometrically at 239 nm.

Table: 4.4 Standard calibration curve of AHD Y in Phosphate buffer pH 6.8 at 239nm

Sr. No.	Concentration (µg/ml)	Absorbance			Average Absorbance
		1	2	3	
1	0	0	0	0	0
2	2	0.0594	0.0648	0.0636	0.0626
3	4	0.1259	0.1215	0.1279	0.1251
4	6	0.1891	0.1929	0.1817	0.1879
5	8	0.2516	0.2479	0.2536	0.2511
6	10	0.3103	0.3177	0.3143	0.3141
7	12	0.3762	0.3824	0.3721	0.3769
8	14	0.4501	0.4528	0.4459	0.4496

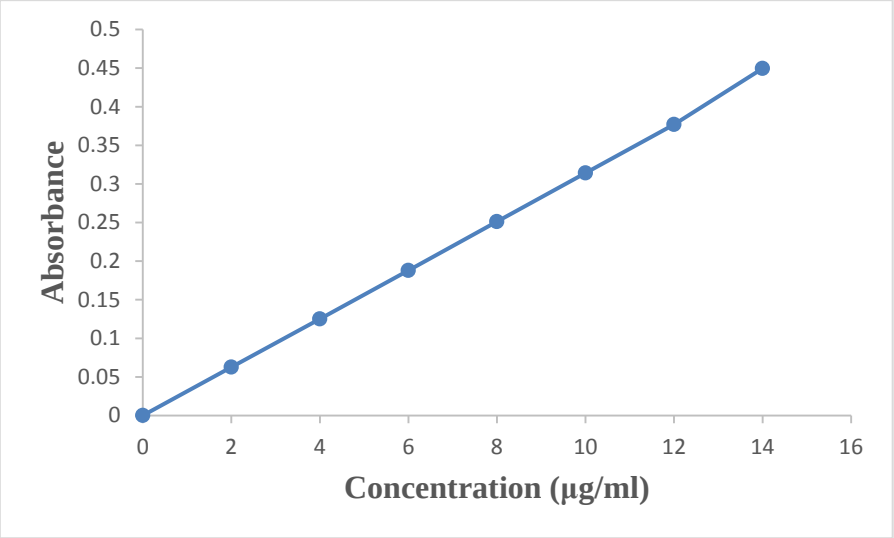


Figure 4.6: Standard Calibration curve of AHD Y in 6.8 phosphate buffer solution

Standard calibration curve of AHD Y in 6.8 phosphate buffer solution was prepared by plotting graph of absorbance vs. concentration. The absorbance of the sample solution was measured at λ_{max} 239 nm (Figure 4.6). A linear plot was obtained as shown in figure 4.6 that gives following linear equation, y = 0.0318x - 0.002 and R^2value was 0.9997.

4.4. Preformulation study

Preformulation studies are the first step in the rational development of dosage form of a drug substance. The objective of preformulation studies is to develop a portfolio of information about the drug substance, so that this information useful to develop different dosage forms. Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients.

4.4.1. Identification of Drug by FTIR:

The Fourier transform infrared spectrum of moisture free powdered sample of AHD X and AHD Y was recorded on IR spectrophotometer (shimadzu) by potassium bromide (KBr) pellet method. The characteristics peaks of different functional group were compared with reported standard peak.

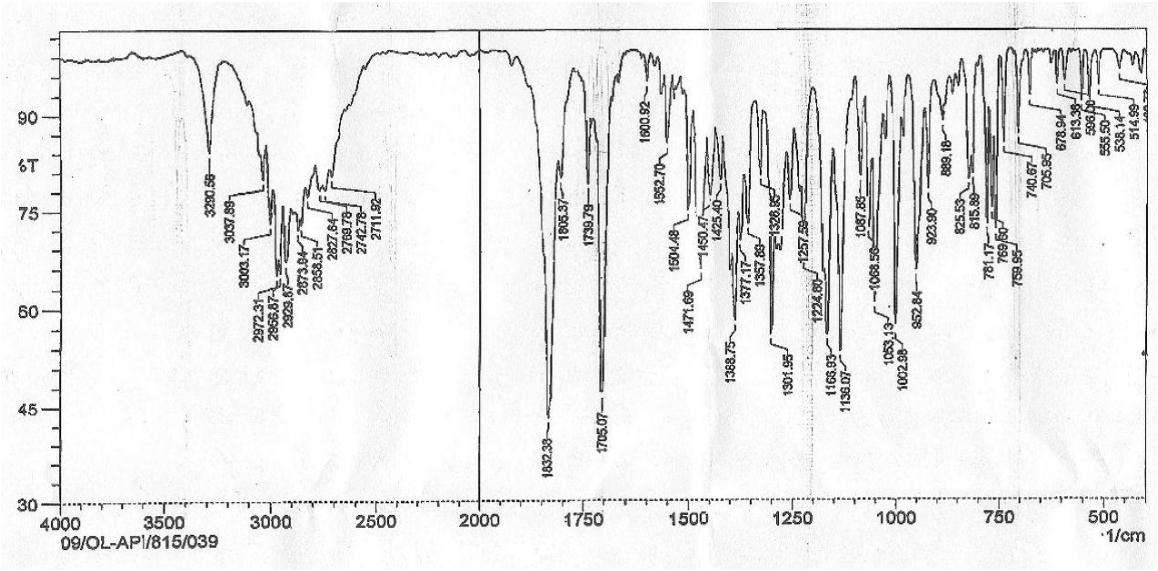


Figure 4.7: FT-IR Spectra of AHD X

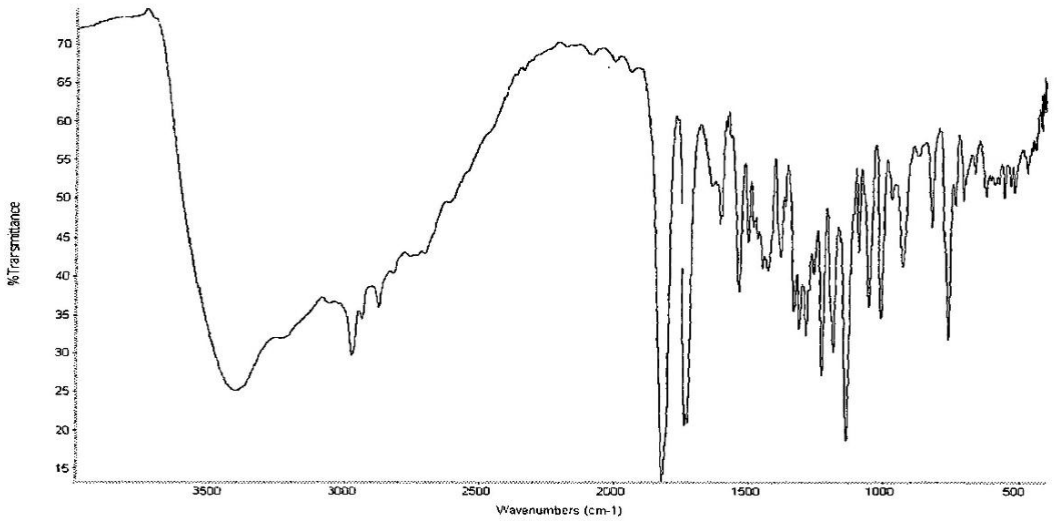


Figure 4.8: FT-IR Spectra of AHD X Reference

Table 4.5 Interpretation of FT-IR Spectra of AHD X

Frequency(cm^{-1})	Assignment
3290.56	-OH Streching
2973.31	Aromatic C-H stretch
2873.94	C-H stretch
1832.38	O-C=O Strech
1705.07	O_2-C=O Strech

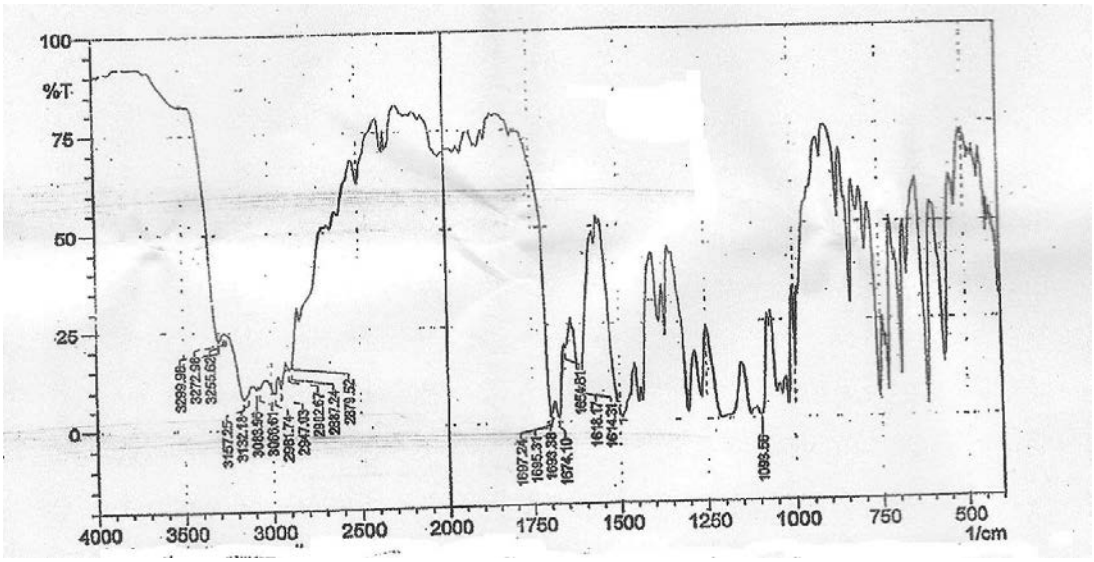


Figure 4.9: FT-IR Spectra of AHD Y

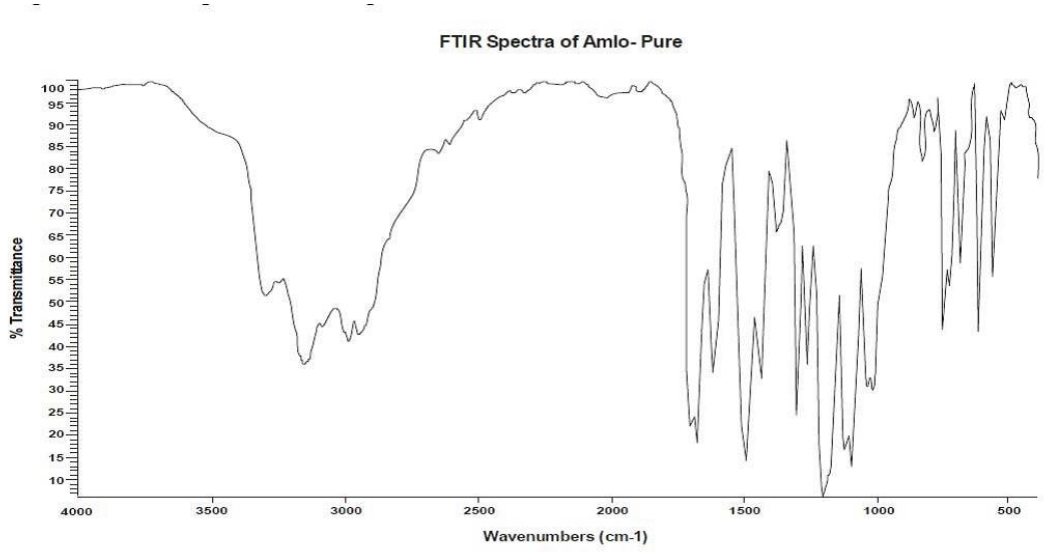


Figure 4.10: FT-IR Spectra of AHD Y Reference

Table 4.6 Interpretation of FT-IR Spectra of AHD Y

Frequency(cm^{-1})	Assignment
2981.74	-C-H Strech
1693.38 ; 1695.31	>C=O Strech
1614.31	-N-H stretch

The FT-IR spectrum shows characteristic peaks corresponding to various functional groups present in AHD X and AHD Y structure. Various functional groups and their respective peaks were illustrated in the table 4.5 and 4.6, which were identical to the reference spectra so, it proves purity of test sample of AHD X and AHD Y.

4.4.2. Physical Characterization of API:

4.4.2.1. Organoleptic Properties:

This includes recording of colour, odour and taste of the drug using descriptive terminology. Record of colour of early batches is very useful in establishing appropriate specifications for later production. Drugs generally have a characteristic odour and taste.

Table 4.7: Organoleptic Properties

PROPERTY	AHD X	AHD Y
Color	White crystalline Powder	White Powder
Odor	Characteristic	Characteristic

4.4.2.2. Solubility Study[32]

The solubility of AHD X and AHD Y was determined in Water, Ethanol and 0.1N HCL. The solubility of AHD X and AHD Y was determined in water, ethanol (95%) and 6.8 pH phosphate buffer by adding an excess amount of drug to tube containing 1 ml of media. Drug was added gradually due to significantly high solubility.

Desriptive term	Parts of solvents required for 1 part of solute
Very soluble	<1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10000
Insoluble	>10000

Table 4.8: Solubility Study

Media	Solubility (AHD X) mg/ ml	Solubility (AHD Y) mg/ ml
95% Ethanol	0.12	0.40
Water	0.01	0.61
pH 6.8 Phosphate Buffer	0.17	1.20
0.1N HCl	1.34	0.94

From the above table we can conclude that AHD X is highly soluble in 0.1 N HCl. Its solubility profile is in following order: 0.1 N HCl> pH 6.8 Phosphate buffer > 95% ethanol > Water.

AHD Y is having higher solubility in pH 6.8 phosphate buffer solution. Its solubility in following order : pH 6.8 Phosphate buffer > 0.1 N HCl> Water > 95% ethanol.

4.4.2.3. Flow property of API[32]

The flow properties from a material result from many forces. There are many types of forces that can act between solid particles: frictional forces, surface tension forces, mechanical forces caused by interlocking of particles of irregular shapes, electrostatic forces and cohesive or van der-vaals forces. These forces can affect granule properties such as particle size, particle size distribution, particle shape, surface texture or roughness, residual surface energy and surface area.

Table 4.9: Flow Property of Drug

Ingredients	Bulk Density (gm/ml)	Tapped Density (gm/ml)	% Carr's index	Hausner's Ratio	Angle of repose
AHD X	0.26	0.42	32.09	1.61	57.9
AHD Y	0.21	0.31	32.25	1.41	39.4

From the above table AHD X and AHD Y is very poor flow property. It is also having poor compression index, so difficulty in compression by direct compression method. They are very fluffy material so additional diluent required for compressibility.

Trial	Flow Property
F1	Good
F2	Good
F3	Good
F4	Good
F5	Good
F6	Good
F7	Good
F8	Good
F9	Good
F10	Good
F11	Good

4.4.2.4. Bulk density[32]: It can be measured by known mass of powder sample that has been passed through a screen into a graduated cylinder. For determining bulk density 100 ml of measuring cylinder was taken and weight of empty cylinder was noted, then sample mass of powder was filled sufficient to produce volume of 100 ml without compacting. Then weight of cylinder was again noted, weight of empty cylinder was subtracted from the total weight. The final weight (mass) was divided by 100 ml (volume) which gave bulk density. Bulk density is calculated by following given formula:

$$\textbf{Bulk density} = \frac{\text{Final Volume of Wt of powder}}{\text{Volume of powder}} \qquad \textbf{.....}\text{Equation 4.1}$$

Trial	Bulk Density (g/ml)(n=3)
F1	0.51 ± 0.02
F2	0.52 ± 0.01
F3	0.50 ± 0.04
F4	0.51 ± 0.03
F5	0.50 ± 0.08
F6	0.57 ± 0.09
F7	0.56 ± 0.03
F8	0.52 ± 0.02
F9	0.48±0.01
F10	0.51±0.03
F11	0.48±0.08

4.4.2.5. Tapped density[32]: Carefully level the powder without compacting as bulk density test and read unsettled apparent volume to the nearest graduated unit. Tap the cylinder mechanically containing sample by raising the cylinder and allowing it to drop its own weight using a suitable mechanical tapped density tester that provides a fixed drop of 14 ± 2 mm at nominal rate of 300 drops per minute. Unless otherwise specified, tap the cylinder 500 times initially and measure the tapped volume to the neares graduated unit. Repeat the tapping an additional 750 times and measure tapped volume to the nearest graduated units. If the differences between the two volumes is less than 2% then final the volume. Calculate the tapped bulk density in gm/ml by the following formula:

$$\textbf{Tapped Density} = \frac{\text{Wt of powder}}{\text{Tapped Volume of powder}} \quad \textbf{.....}\text{Equation 4.2}$$

Trial	Tapped Density (g/ml)(n=3)
F1	0.67 ± 0.05
F2	0.64 ± 0.02
F3	0.65 ± 0.07
F4	0.64 ± 0.01
F5	0.67 ± 0.03
F6	0.66 ± 0.08
F7	0.66 ± 0.04
F8	0.6 ± 0.04
F9	0.57±0.07
F10	0.62±0.01
F11	0.59±0.03

4.4.2.6. Angle of Repose[32]**:** Angle of repose is the tan inverse of angle between height of pile of powder and the radius of the base of conical pile.

The maximum slope, measured in degrees from the horizontal, at which loose solid material will remain in place without sliding.

$\theta = \tan^{-1} h/r$ …..Equation 4.3

Where h = height of pile of powder; and r = radius of the base of conical pile

Values for angle of repose less than or equal to 30 degrees suggest a free flowing material and angles greater than or equal to 40 degrees suggest a poorly flowing material. Hopper flow rate measurement is also a method for measuring flow ability.

Table 4.10: Correlations between Angle of Repose and Flow Property

Angle of Repose, Ɵ	Predicted Flow Property
25-30	Excellent
31-35	Good
36-40	Fair (Aid not needed)
41-45	Passable(May Hang up)
46-55	Poor(Must agitate or vibrate)
>56-65	Very poor

Trial	Angle of Respose (n=3)
F1	27.11 ± 0.01
F2	28.95 ± 0.08
F3	27.75 ± 0.05
F4	29.13 ± 0.02
F5	32.92 ± 0.01
F6	26.25 ± 0.07
F7	25.56 ± 0.08
F8	27.26 ± 0.06
F9	28.62±0.05
F10	29.43±0.02
F11	29.37±0.01

4.4.2.7. Carr's Compressibility Index (CI)[32]:

Compressibility is indirectly related to the relative flow rate, cohesiveness and particle size distribution of the powder. Powders with compressibility values lesser than about 20% have been found to exhibit good flow properties. Tapped (ρ2) and Apparent (ρ1) Bulk density measurements can be used to estimate the compressibility of a material.

Carr's Compressibility index (%) = $\frac{\rho 2-\rho 1}{\rho 2}$ X 100 …..Equation4.4

The Carr's index is a one point determination and does not reflect the ease or speed with which consolidation occur. Indeed some materials have high index suggesting poor flow but may consolidate rapidly, which is essential for uniform filling on tablet machines when the power flows at nearly equal to bulk density in to the die and consolidates to approaching tapped density prior to compression.

Table 4.11: Scale of Flow ability by Carr's Compressibility Index

C.I.	Category
<10	Excellent
11 – 15	Good
16 – 20	Fair
21 – 25	Passable
26 – 31	Poor
32 – 37	Very poor
>38	Very poor

Trial	Carr's Index (n=3)
F1	23.88 ± 0.01
F2	18.75 ± 0.09
F3	23.076 ± 0.04
F4	20.31 ± 0.07
F5	25.37 ± 0.05
F6	13.64 ± 0.03
F7	13.81 ± 0.01
F8	13.33 ± 0.05
F9	15.25±0.04
F10	17.39±0.07
F11	18.53±0.05

4.4.2.8. Hausner's Ratio[32]:

It is the ratio of bulk volume to tapped volume or tapped density to bulk density. Hausner's ratio is an important character to determine the flow property of powder and granules. This can be calculated by the following formula-

$$\textbf{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \qquad \text{.....Equation 4.5}$$

Table 4.12: Hausner's Ratio

Flow Character	Hausner's Ratio
Excellent	1.00–1.11
Good	1.12–1.18
Fair	1.19–1.25
Passable	1.26–1.34
Poor	1.35–1.45
Very poor	>1.46–1.59

4.4.2.9. Melting Point: Melting point of the drug was determined by using melting point apparatus. This was compared with the official melting point value of drug.

	Melting Point of drugs (obtained)	Melting Point (official)
AHD X	178°C	175-180°C
AHD Y	198°C	195-204°C

4.4.2.10. Moisture Content: Moisture content of the drug was determined by using helogen moisture Analyzer and karl Fisher reagent technique. Value was compare with Certificate of quality analysis report.

Table 4.13: Moisture Content

Method	AHD X	AHD Y
Halogen Moisture Analyzer	0.42% w/w	0.26 % w/w
Water by KF Method	0.11% w/w	0.06% w/w

4.4.2.11. Particle size analysis:

Various physical and chemical properties of drug substances are affected by their particle size distribution and shape. In order to assure consistent product quality, the particle size of the API has been characterized. From the results obtained, the limits will be derived which will be routinely applied by the dosage form manufacturer during analysis of API.

In case of highly soluble drugs, the particle size does not affect the dissolution but in case of low soluble drugs, particle size can affect dissolution rate and bioavailability. AHD X is BCS class 2 drug so it is essential to determine particle size that affect dissolution property.

The particle size distribution of API was determined by Malvern analyser.

Table: 4.14: Malvern Particle size Analysis of Drug

Method	AHD X	AHD Y
Particle Size	d10= 3µm d50= 7µm d90= 19µm	d10= 1µm d50= 3µm d90= 6 µm

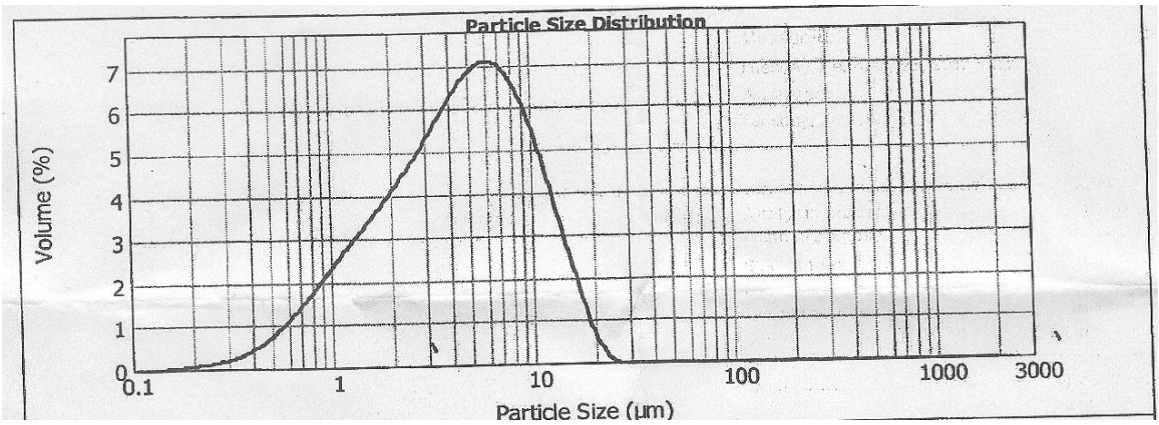


Figure 4.11: Malvern Plot of AHD X

Table 4.15: Various parameters used in determination of particle size distribution (PSD) by Malvern analyser.

Method	Wet method
Instrument	Malvern master sizer (HYDRO 2000S)
Analysis model	General purpose
Dispersion media	Water
Particle RI	1.53
Absorption	0.1
Dispersion RI	1.33
Obscuration	10.0-20.0 %
Speed	2500
Measurement time	12 sec
Background time	12 sec
Sweep	12000

Sample preparation:

Fill the sample cell with water, add 3 drops of Tween 80, align the sizer and measure the background. With spatula add sample into the sample cell until proper obscuration is achieved (10.0-20.0 %). Align the system and measure the background. Wait 1 minute for the obscuration to stabilized and start measurement.

4.4.3. Drug Excipient Compatibility Study:

Table 4.16: Ratio of Drug and Excipients in Physical Compatibility Study with AHD X

Sl. No.	Ingredient	Ratio	25°C & 60% RH 1 Month	40°C & 75% RH 1 Month
1	AHD X (Drug X)	1:1	NC	NC
2	AHD X + MCC 101	1:1	NC	NC
3	AHD X + MCC 112	1:1	NC	NC
4	AHD X + Mannitol 25C	1:1	NC	NC
5	AHD X + Mannitol SD 200	1:1	NC	NC
6	AHD X + LHPC LH 11	1:1	NC	NC
7	AHD X + Pregeletinised Starch (Lycatab PGS)	1:1	NC	NC
8	AHD X + Pregeletinised Starch 1500 LM	1:1	NC	NC
9	AHD X + Corn Starch	1:1	NC	NC
10	AHD X + Colloidal Silicone Dioxide	1:1	NC	NC
11	AHD X + Stearic Acid 95	1:1	NC	NC
12	AHD X + Poloxamer 407	1:1	NC	NC
13	AHD X + SLS	1:1	NC	NC
14	AHD X + Vit E TPGS	1:1	NC	NC
15	AHD X + Lactose Monohydrate (Pharmatose 200)	1:1	NC	NC
16	AHD X + Lactose Anhydrous (DCL 21)	1:1	NC	NC
17	AHD X + Silicified MCC (PROSOLVE SMCC HD 90)	1:1	NC	NC
18	AHD X + Magnesium Stearate	1:1	NC	NC
19	AHD X + OPADRY ® Orange	1:1	NC	NC

Table 4.17: Ratio of Drug and Excipients in Physical Compatibility Study with AHD Y

Sl. No.	Ingredient	Ratio	25°C & 60% RH 1 Month	40°C & 75% RH 1 Month
1	AHD Y (Drug Y)	1:1	NC	NC
2	AHD Y + MCC 101	1:1	NC	NC
3	AHD Y + MCC 112	1:1	NC	NC
4	AHD Y + Mannitol 25C	1:1	NC	NC
5	AHD Y + Mannitol SD 200	1:1	NC	NC
6	AHD Y + LHPC LH 11	1:1	NC	NC
7	AHD Y + Pregeletinised Starch (Lycatab PGS)	1:1	NC	NC
8	AHD Y + Pregeletinised Starch 1500 LM	1:1	NC	NC
9	AHD Y + Corn Starch	1:1	NC	NC
10	AHD Y + Colloidal Silicone Dioxide	1:1	NC	NC
11	AHD Y + Stearic Acid 95	1:1	NC	NC
12	AHD Y + Poloxamer 407	1:1	NC	NC
13	AHD Y + SLS	1:1	NC	NC
14	AHD Y + Vit E TPGS	1:1	NC	NC
15	AHD Y + Lactose Monohydrate (Pharmatose 200)	1:1	NC	NC
16	AHD Y + Lactose Anhydrous (DCL 21)	1:1	NC	NC
17	AHD Y + Silicified MCC (PROSOLVE SMCC HD 90)	1:1	NC	NC
18	AHD Y + Magnesium Stearate	1:1	NC	NC
19	AHD Y + OPADRY ® Orange	1:1	NC	NC

Testing Frequency

Analysis of drug- excipients compatibility study was done at;

1. At initial stage
2. After 1 month at 25±2 ^{0}C / 60±5 %RH
3. After 1 month at 40±2 ^{0}C / 75±5 %RH

Physical Observation

Physical observation of sample was done at every week for any color change.

4.4.3.1. Active Pharmaceutical Ingredient weight adjustment in dose:

AHD X molecular weight is prodrug. This is design for enhance permeability. AHD X molecular weight is 558.585 g/mol. This is equivalent to 446.5016 g/mol AHD X. This does not required because prodrug is active molecule.

AHD Y is a salt form so it required to calculate to active drug moiety in dosage form. AHD Y have molecular weight is 585.07 g/mol which is equivalents to 408.876 g/mol. Calculate AHD Y weight equivalents to 10mg AHD Y.

4.5. For preparation of Immediate Release tablets of AHD X and AHD Y various methods such as Wet Granulation method & Dry Granulation method are evaluated.

4.5.1. Wet Granulation method:

Wet granulation is a procedure of utilizing a fluid fastener to daintily agglomerate the powder blend. The measure of fluid must be appropriately controlled, as over-wetting will bring about the granules to be too hard and under-wetting will make them be too delicate and friable. Fluid arrangements have the upside of being more secure to manage than dissolvable based frameworks yet may not be reasonable for medications which are corrupted by hydrolysis.

Procedure:

Weigh all ingredient. AHD X, AHD Y, Mannitol (Pearlitol 25C), Microcrystalline Cellulose 101 and Low substituted Hydroxy Propyl Cellulose (LH-11) shifted through 40# sieve. Mix all ingredients in polybag for 10 minutes. Transfer all material in Rotatory mixture granulator (RMG). Make 7% w/w corn starch or pregelatinised starch solution by using hot water of 65 ~ 70° C. Mix ingredient in RMG by on chopper motor for 10 min. Add starch solution gradually and start chopper on an appropriate rotation to break lumps. Stop impeller and chopper motor after completing addition. Granules passed through 1.413µm screen in Quadro® comill for uniform granules. Granules are transferred in rapid dryer for drying. Dry granules till LOD reduce up to 1.5 – 2.5 %w/w. Granules passed through 24# sieve.

Mannitol (Pearlitol SD200), LHPC (LH-11) and colloidal anhydrous silica are passed through 40# sieve. Stearic acid and magnesium stearates are passed through 60# sieve. Shifted material added to above granules and transfer all material to cage blender. Rotate material for 10 min at 18 rpm. Compress tablet by using 9.00 mm round bevel shapped, plain bottom punch and upper punch embossed 930 in D tooling. Hardness of the tablets was maintained at 7-8 Kg/cm2 and tablet weight at 300 mg.

Mechanism of Wet granulation

1. Nucleation
2. Transition in the funicular and capillary stage
3. Ball growth.

In nucleation, the formation starts with loose agglomerates or single particles which are wetted by the binding solution and form small granules by pendular bridging.

Continued addition of binding solution and tumbling action consolidates and strengthens the granules through the funicular stage and into the capillary stage.

In this transition stage the granules continue to grow by one of two mechanisms:

(1) Single particle addition and

(2) Multiple granule formation.

Theoretically, at the end of the transition stage ball formation occur i.e. there are a large number of small granules with a fairly wide size distribution.

4.5.2. Dry Granulation method:

In dry granulation handle the powder blend is compacted without the utilization of warmth and dissolvable. The two essential methodology are to shape a minimized of material by pressure and after that to process the smaller to acquire granules.

Two techniques are utilized for dry granulation. The all the more broadly utilized technique is slugging, where the powder is precompressed and the subsequent tablets or slugs are processed to yield granules. The other strategy is to precompress the powder with weight moves utilizing a machine, for example, Chilosonator.

Two main dry granulation processes:

a. Slugging process

Granulation by slugging is the process of compressing dry powder of tablet formulation with tablet press having die cavity large enough in diameter to fill quickly. The accuracy or condition of slug is not too important. Only sufficient pressure to compact the powder into uniform slugs should be used. Once slugs are produced they are reduced to appropriate granule size for final compression by screening and milling.

b. Roller compaction

The compaction of powder by method for weight roll can likewise be expert by a machine called Chilosonator. Not at all like tablet machine, the Chilosonator turns out a compacted mass in an enduring consistent stream. The powder is encouraged down between the rollers from the container which contains a winding wood screw to sustain the powder into the compaction zone. Like slugs, the totals are screened or processed for generation into granules.

Procedure

Weigh all above interagranuler material accurately. Pass all material except magnesium stearate passed through 40# sieve. Magnesium stearate passed through 60# sieve. Mix all ingredient in polybag by hand mixing for 15 minutes. Material transfer to the roller compacter for making compacts. Collect compact & fines and separate it using 14# sieve. Compacts are transferred into QUADRO® co mill for milling. First all compacts are passed through 6.016mm screen at low speed for reducing time. These small compacts material again passed through 1.124mm sieve to convert them into granules. These granules are transferred into vibrating sieve shaker to shift them in 80# sieve. Retained material is collected as granules and passed material is collected as a fines. These fines are added to 14# passed fined producing in roller compacter. Repeat cycle until granules and fines ratio achieved up to 50:50.

Weigh all above extra granules material. Pass all material except magnesium stearate passed through 40# sieve. Magnesium stearate passed through 60# sieve. These are transferred into above granules. Mix them into polybag for 10- 15 min.

Compress tablet by using 9.00 mm round bevel shaped, plain bottom punch and upper punch embossed 930 in D tooling. Hardness of the tablets was maintained at 7-8 Kg/cm2 and tablet weight at 300 mg. Coat the tablet as described in previous batch.

4.6. Evaluation of tablet:

Prepared powder blends were evaluated for the following parameters.

4.6.1. Precompression parameters:

All precompression parameter including bulk density, tapped density, Compressibility index Hausner ratio and Angle of repose were evaluated as per section 5.7.2.3. Flow properties of drugs.

4.6.2. Post compression parameters:

Prepared tablet was evaluated for the following parameters.

1. Thickness

Thickness of tablet can be measured by using vernier calipers from the center of top and bottom part of the tablet.

2. Uniformity of Weight[32]:

Weigh individually 20 units selected at random or, for single dose preparations in individual containers, the contents of 20 units, and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the table and none deviates by more than twice that percentage.

Table 4.18: IP limits for weight variation[32]

Average weight of tablet	Percentage deviation
80 mg or less	10
More than 80 mg but less than 250 mg	7.5
250 or more	5

3. Hardness[32]:

The breaking force of tablets is commonly called hardness in the pharmaceutical literature; however, the use of this term is misleading. In material science, the term

hardness refers to the resistance of a surface to penetration or indentation by a small probe. The term crushing strength is also frequently used to describe the resistance of tablets to the application of a compressive load. Although this term describes the true nature of the test more accurately than does hardness, it implies that tablets are actually crushed during the test, which often is not the case. Moreover, the term strength in this application can be questioned, because in the physical sciences that term is often used to describe a stress (e.g., tensile strength). Thus, the term breaking force is preferred and will be used in the present discussion. Some of the modern measuring devices used are Monsanto, Pfizer and Erweka hardness tester.

Modern breaking force testers are usually calibrated in kiloponds or newtons. The relationship between these units of force (3) is 1 kilopond (kp) = 1 kilogram-force (kgf) = 9.80 N. The test results should be expressed in standard units of force which facilitate communication. Some breaking force testers also will provide a scale in Strong Cobb units (SCU), a carryover from the days when Strong Cobb hardness testers were in common usage.

4. Friability test[32]:

For tablets with an average weight of 0.65 g or less take a sample of whole tablets corresponding to about 6.5 g and for tablets with an average weight of more than 0.65g take a sample of 10 whole tablets. Dedust the tablets carefully and weigh accurately the required number of tablets. Place the tablets in the drum and rotate it 100 times. Remove the tablets, remove any loose dust from them and weigh them accurately. The test is run only once unless the results are difficult to interpret or if the weight loss is greater than the targeted value, in which case, the test is repeated twice and the mean of the three tests is determined. A maximum loss of weight (from a single test or from the mean of the three tests) not greater than 1.0 per cent is acceptable for most tablets. Following formula was used to calculate the friability

Friability = $[(W_1-W_2)100]/W_1$

Where,

W_1= Weight of tablet before test

W_2 = Weight of tablet after test

5. Disintegration test[32]:

The USP device to rest disintegration was six glass tubes that are 3 inch long, open at the top, and held against 10 mesh screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1 liter beaker of distilled water at 37± 2 °C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.

6. Drug content:

20 tablets were selected randomly and triturated. A quantity of this powder corresponding to 300 mg was dissolved in 40 ml of methanol, sonicate for 5 mins and cool to room temperature dilute with methanol upto the 100 ml. transfer 5 ml of this solution to 100 ml volumetric flask and dilute upto the mark, mix and pass through filter having 0.45 µm or finer porosity. Evaluate by usin HPLC condition

7. *In-vitro* Dissolution

Dissolution medium: 900 ml of 6.8 phosphate buffer solution

Temperature: 37 ± 0.5°C

RPM: 50 rpm

Time: 45 min

Apparatus: USP Type-II (Paddle)

Aliquots of 5 ml was withdrawn at regular time intervals and were replaced immediately with same volume of fresh buffer medium. Aliquots, following suitable dilutions were assayed by HPLC method.

4.7. Comparison of Formulated Dosage Form with Innovator Product:

Optimized formulation was selected for comparison with marketed formulation of AHD X and AHD Y. The parameters compared with Innovator formulations are disintegration test, wetting time and % drug release study.

4.8. Comparison of Dissolution Profiles:

The similarity factor (f_2) given by SUPAC guidelines for modified release dosage form was used as a basis to compare dissolution profile. The dissolution profiles are considered to be similar when f_2 is between 50 and 100. The dissolution profiles of products were compared using f_2. This similarity factor is calculated by following formula,

$$\mathbf{f2 = 50 \times \log \{[1+(1/n) \sum_{j1}^{n} | Rj - Tj | 2] - 0.5 \times 100\}} \quad \text{.....Equation4.1}$$

Where,

n = number of time points

R_j= Dissolution value of the reference batch at time t

T_j = Dissolution value of the test batch at time t

4.9. Stability Studies:

Stability studies on the optimized formulation was carried out to determine the effect of presence of formulation additives on the stability of the drug and also to determine the physical stability of the formulation under accelerated storage conditions.

The tablets were stored in an aluminium-aluminium blister and subjected to elevated temperature and humidity conditions of 40 ± 2^{o}C/ 75 ± 5 % RH for time period of 4 weeks (nearly a month).

Samples were withdrawn at the end of every week and evaluated for

- Disintegration Time
- % Drug content
- % Drug release

Table 4.19: Formula for coating process

SI. NO.	Ingredient	Weight (mg)
1	Core tablet	300mg
2	OPADRY ® Orange (HPMC Based)	8mg
Total		308mg

Coating solution preparation:

The coating solution was prepared by adding OPADRY® (HPMC based) in purified water under continuous stirring using mechanical stirrer. The concentration of coating solution prepared was 14% w/v. 20% w/v extra quantity of total coating solution was taken to compensate the loss of coating solution during process.

Table 4.20: Coating parameter for direct compression approach

Parameters	Conditions
Pan speed	1-5 rpm
Inlet air temperature	30-70 °C
Atomisation air pressure	1.0 kg/cm^2
Peristaltic pump speed	1-20 rpm
Bed temperature	35-45 °C
Exhaust temperature	30-60 °C
Spray rate	2-5 gm/min
Nozzle size	1 mm
Distance of bed to gun	20 cm
Coating solution	14 OPADRY Orange in water

5. Result & Discussion

5.1. Formulation of Immediate Release Tablet of AHD X AND AHD Y by using Wet Granulation & Dry Granulation Method

5.1.1. Formulation and development of AHD X and AHD Y by Wet Granulation Technique (F1 & F2) for selection of binder.

Table 5.1: Composition of Core Tablet (F1 & F2)

INGRIDIENT	**F1 mg/tab**	**F2 mg/tab**
INTRAGRANULER PART (WET GRANULATION)		
AHD X	40.000	40.000
AHD Y	13.870	13.870
Mannitol (Pearlitol 25C)	101.130	101.130
Microcrystalline Cellulose 101D	20.000	20.000
LHPC LH11	45.000	45.000
Corn Starch	10.000	-
Pregelatinised Starch	-	10.000
Purified Water	QS	QS
Total	**230.000**	**230.000**
EXTRAGRANULER PART		
Mannitol (Pearlitol SD200)	42.500	42.500
LHPC LH11	15.000	15.000
Colloidal Anhydrous Silica	3.000	3.000
Stearic Acid 95	8.000	8.000
Magnesium Stearate	1.500	1.500
Total	**300.000**	**300.000**

LHPC LH11= Low substituted Hydroxypropyl Cellulose

Table 5.2: Post Compression Evaluation

Trial	Diameter (mm)	Thickness (mm)	Weight Variation (mg)	% Friability
F1	9.03	5.01 ±0.6	300 ± 0.8	1.15
F2	9.03	5.06 ±0.6	301.5 ± 0.4	0.986

Trial	Disintegration Time (min.sec)	Hardness (kp)	Drug Content (AHD X)	Drug Content (AHD Y)
F1	7.34	7.0±0.14	80.60%	67.20%
F2	5.45	6.5±0.18	87.65%	68.91%

In F1 batch, % friability is more than 1.0 (0.5 to 1% as per USP), Disintegration time and Hardness do not meet to the requirement. Where Drug Content of AHD X & AHD Y is very less.*

In F2 batch, Disintegration time is increase and hardness is decrease. Also the Drug Content level is very less in both the drugs. Need to decrease the Disintegration time by optimizing different concentration of disintegrant and binder in next batches.

***** Innovator formulation: Disintegration Time-Around 1 min., Hardness- 7.5-9.5

5.1.1.1. *In-vitro* drug release of AHD X and AHD Y

Time (min)	Drug X		Drug Y	
	F1	F2	F1	F2
0	0	0	0	0
5	22.6	21.8	15.8	16.5
10	32.8	34.6	21.6	22.6
15	46.8	49.8	32.6	34.8
20	53.2	56.9	44.9	44.9
25	61.9	66.8	52.6	55.6
30	68.2	73.9	55.6	61.9
45	72.6	83.9	59.1	65.4

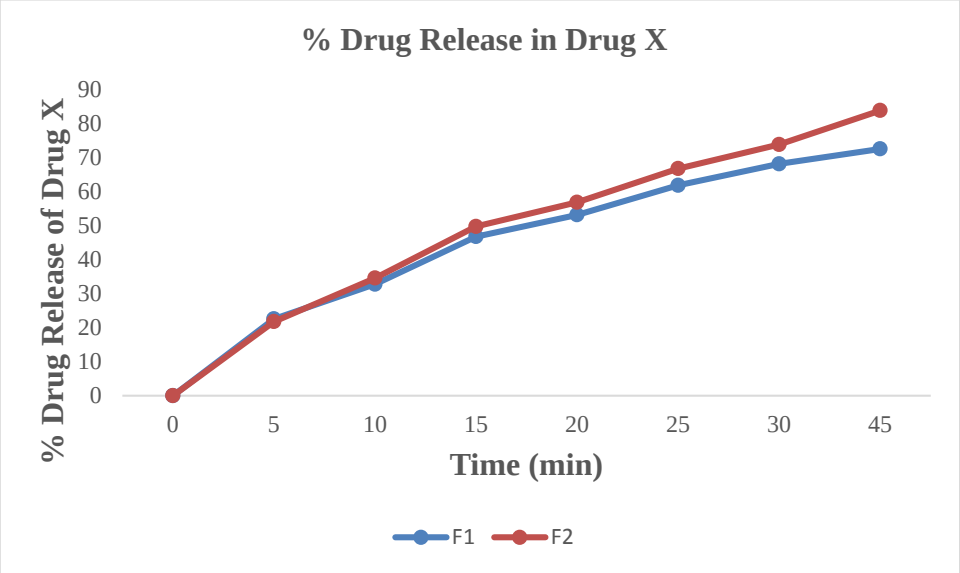


Figure 5.1:Drug Release of AHD X in 6.8 pH Phosphate Buffer Solution

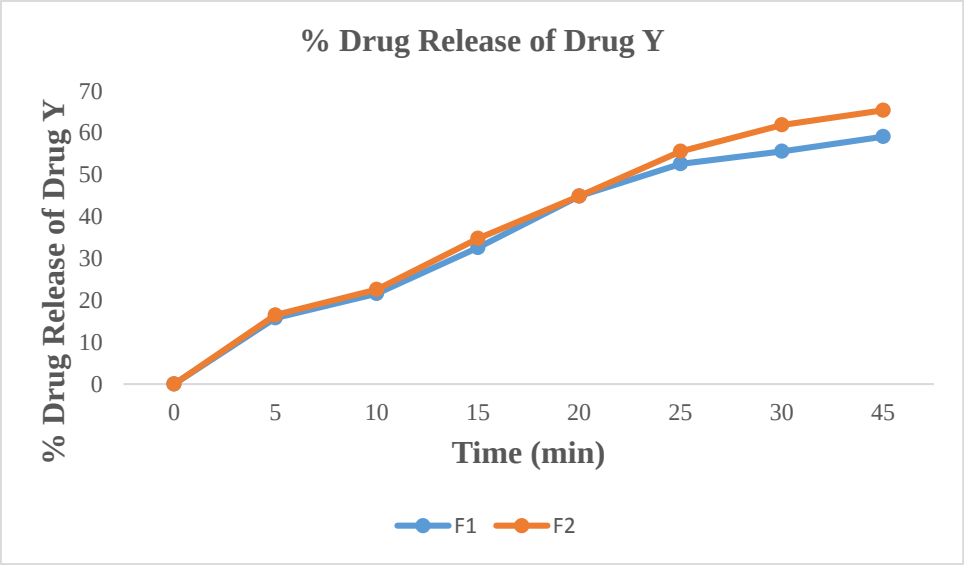


Figure 5.2:Drug Release of AHD Y in 6.8 pH Phosphate Buffer Solution

Drug X & Y:

From the above dissolution data we can concluded that, **F1 & F2 batch** is having poor result in dissolution. Compare to F1 batch, F2 batch having good drug release.

F1 batch tablet are having poor flow and friable tablet. So **Pregelatinised starch** is good binder for compression.

5.1.2. Formulation and development of AHD X and AHD Y by Wet Granulation Technique (F3 to F5) for selection of solubilizer.

Table 5.3: Composition of Core Tablet (F3 to F5)

INGRIDIENT	**F3 mg/tab**	**F4 mg/tab**	**F5 mg/tab**
INTRAGRANULER PART (WET GRANULATION)			
AHD X	40.000	40.000	40.000
AHD Y	13.870	13.870	13.870
Mannitol (Pearlitol 25C)	99.630	99.630	99.630
Microcrystalline Cellulose 101D	20.000	20.000	20.000
LHPC LH11	45.000	45.000	45.000
Poloxamer 407	1.500	-	-
SLS	-	1.500	-
Vitamin E TPGS	-	-	1.500
Pregelatinised Starch (Lycatab PGS)	10.000	10.000	10.000
Purified Water	QS	QS	QS
Total	**230.000**	**230.000**	**230.000**
Extragranuler Part			
Mannitol (Pearlitol SD200)	31.000	31.000	31.000
Lactose Anhydrous (DCL21)	10.000	10.000	10.000
LHPC LH11	15.000	15.000	15.000
Colloidal Anhydrous Silica	3.000	3.000	3.000
Stearic Acid 95	6.000	6.000	6.000
Sodium Stearic Fumarate	3.000	3.000	3.000
Magnesium Stearate	2.000	2.000	2.000
Total	**300.000**	**300.000**	**300.000**

Table 5.4: Post Compression Evaluation

Trial	Diameter (mm)	Thickness (mm)	Weight Variation (mg)	% Friability
F3	9.03	5.02 ±1.6	302 ± 0.72	0.458
F4	9.03	5.05 ±1.8	299 ± 1.2	0.869
F5	9.03	4.96±0.6	301 ± 1.2	0.798

Trial	Disintegration Time (min.sec)	Hardness (kp)	Drug Content (AHD X)	Drug Content (AHD Y)
F3	3.16	7.5±0.04	95.68%	79.61%
F4	3.57	7.0±0.20	94.64%	84.64%
F5	2.13	6.0±0.09	98.92%	86.45%

In F3 batch, here Disintegration time is increase. Where Hardness decreases and the Drug content level of drug AHD Y is very less.*

In F4 batch, here also Disintegration time is increase. Where Hardness decreases and the Drug content level of drug AHD Y is less.

In F5 batch, here the Disintegration time is decrease in compare to above batches but the Hardness of tablet decreases. Where the Drug Content of drug AHD Y is less but drug AHD X is optimum.

% Friability is less than 1% in above all batches. Which is optimum.

***** Innovator formulation: Disintegration Time-Around 1 min., Hardness- 7.5-9.5

5.1.2.1. *In-vitro* drug release of AHD X and AHD Y

Time (min)	Drug X			Drug Y		
	F3	F4	F5	F3	F4	F5
0	0	0	0	0	0	0
5	22.6	19.5	23.8	15.8	27.3	37.2
10	34.8	33.6	56.8	21.5	42.9	44.1
15	43.9	43.8	61.8	31.8	67.8	64.5
20	52.7	57.2	72.5	42.9	76.4	71.9
25	67.4	70.2	86.8	53.1	81.2	83.6
30	78.4	73.5	91.4	62.8	82.5	84.5
45	83.4	78.4	94.5	76.9	83.9	85.7

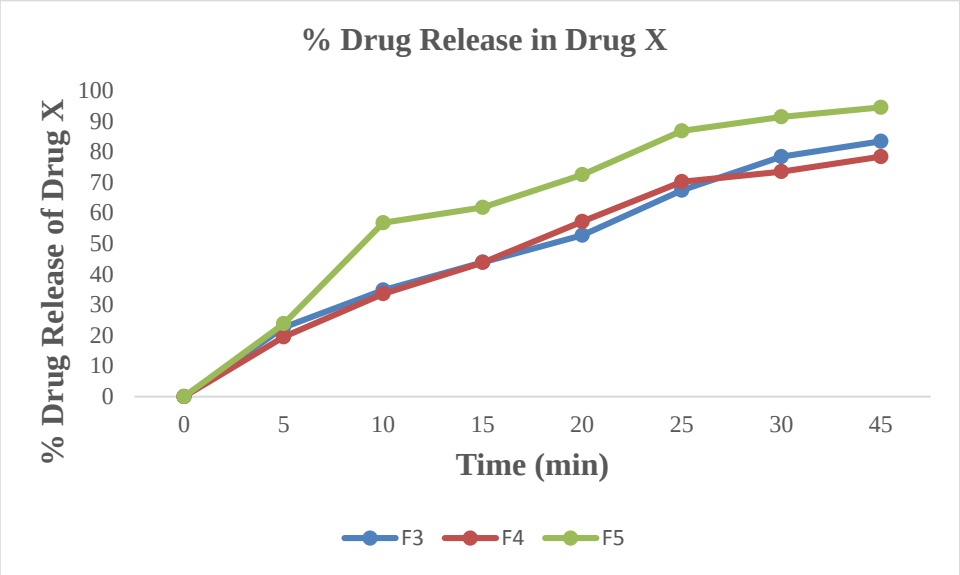


Figure 5.3: Drug Release of AHD X in 6.8 pH Phosphate Buffer Solution

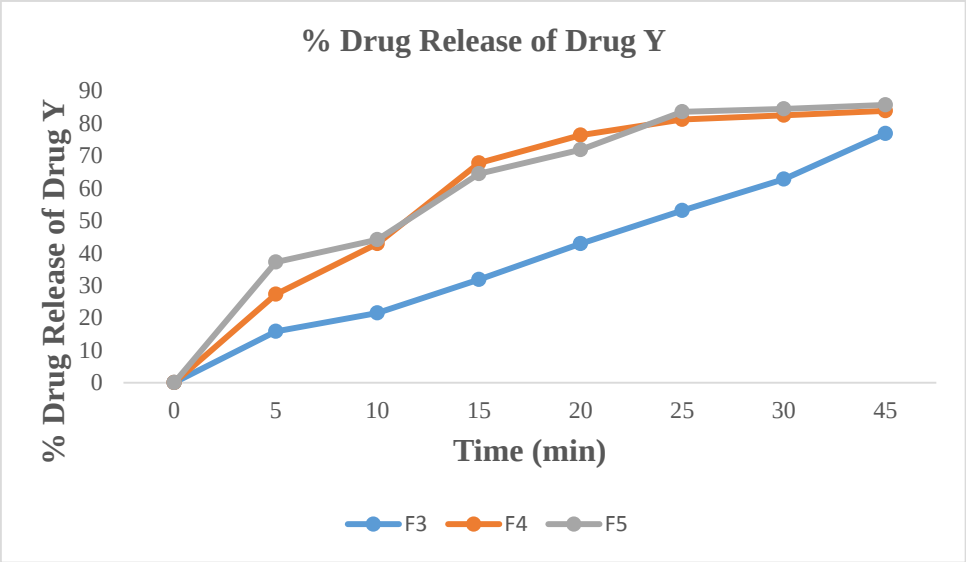


Figure 5.4: Drug Release of AHD Y in 6.8 pH Phosphate Buffer Solution

Drug X & Y:

In batch F3, F4 and F5 design for selection of solubilizes by using Poloxamer 407, SLS, and Vitamin E TPGS. Among all the batches drug release of AHD X plot batch F5 giving higher dissolution profile. So we decide for selection of **Vitamin E TPGS** is having good solubility enhancer of drug and further design to develop it.

5.1.3. Formulation and development of AHD X and AHD Y by Dry Granulation technique (F6 to F8) using various concentration of binder.

Table 5.5: Composition of Core Tablet (F6 to F8)

INGRIDIENT	**F6 mg/tab**	**F7 mg/tab**	**F8 mg/tab**
INTRAGRANULER PART (DRY GRANULATION)			
AHD X	40.000	40.000	40.000
AHD Y	13.870	13.870	13.870
Silicified MCC(PROSOLVE SMCC HD 90)	107.130	102.130	97.130
Pregelatinised Starch 1500 LM	10.000	15.000	20.000
Magnesium Stearate	1.000	1.000	1.000
TOTAL	**172.000**	**172.000**	**172.000**
EXTRAGRANULER PART			
Microcrystllline Cellulose (MCC 112D)	100.000	100.000	100.000
Lactose Anhydrous (DCL 21)	6.000	6.000	6.000
Silicified MCC (PROSOLVE SMCC HD 90)	20.000	20.000	20.000
Magnesium Stearate	2.000	2.000	2.000
TOTAL	**300.000**	**300.000**	**300.000**

Table 5.6: Post Compression Evaluation

Trial	Diameter (mm)	Thickness (mm)	Weight Variation (mg)	% Friability
F6	9.03	4.99±0.6	301 ± 0.8	0.147
F7	9.03	5.01 ±0.8	300 ± 1.2	0.758
F8	9.03	4.98±0.4	301 ± 0.8	0.798

Trial	Disintegration Time (min.sec)	Hardness (kp)	Drug Content (AHD X)	Drug Content (AHD Y)
F6	2.55	8.8 ± 0.08	95.89%	94.56%
F7	2.3	9.9 ± 0.01	94.93%	97.88%
F8	2.07	9.6 ± 0.02	97.67%	99.24%

In F6 batch, here the Hardness of tablet is increase. Disintegration time is as desired. Drug content of both the drugs are almost optimum.*

In F7 batch, here Disintegration time is still increase where the Hardness of the tablet and Drug Content of both the drugs are optimum.

In F8 batch, here the Disintegration time is decrease but not as desired. But Hardness of tablet and Drug Content of both the drugs are as desired.

% Friability is less than 1% in above all batches. Which is optimum.

***** Innovator formulation: Disintegration Time-Around 1 min., Hardness- 7.5-9.5

5.1.3.1. *In-vitro* drug release of AHD X and AHD Y

Time (min)	Drug X			Drug Y		
	F6	F7	F8	F6	F7	F8
0	0	0	0	0	0	0
5	45.6	22.8	30.4	37.2	44.5	48.4
10	58.2	34.8	41.4	48.6	58.6	64.6
15	73.8	43.9	55.7	65.2	67.8	73.2
20	79.4	52.7	62.8	76.4	74.5	77.3
25	80.9	67.4	76.4	79.6	82.6	82.2
30	83.8	78.4	83.9	80.8	91.5	84.2
45	86.7	93.4	95.6	80.4	95.2	97.8

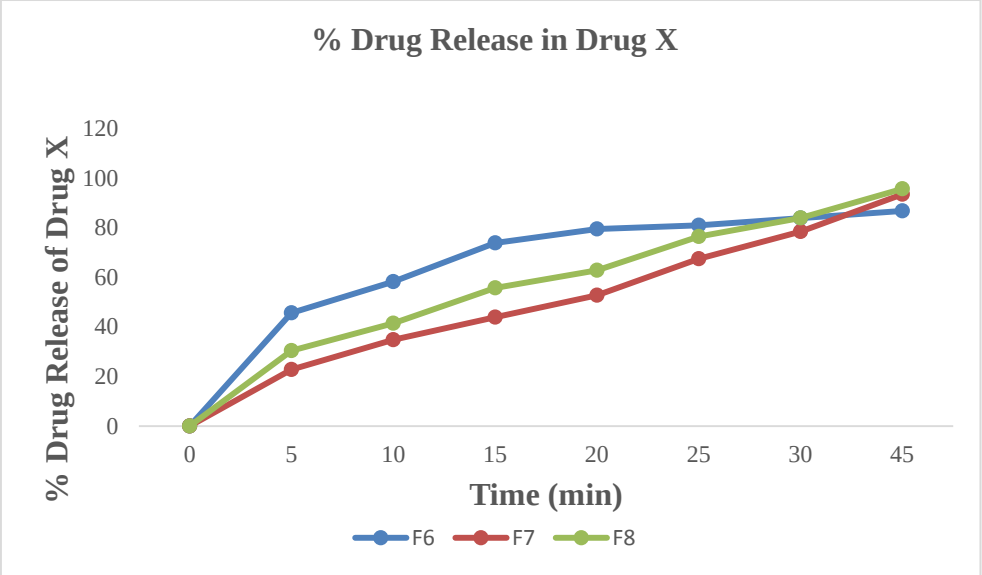


Figure 5.5: Drug Release of AHD X in 6.8 pH Phosphate Buffer Solution

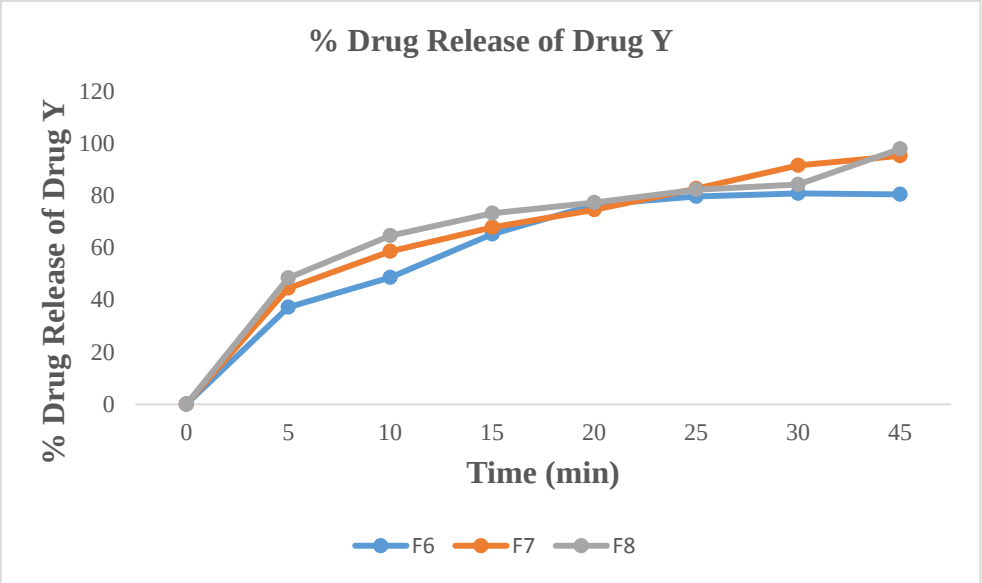


Figure 5.6: Drug Release of AHD Y in 6.8 pH Phosphate Buffer Solution

Drug X:

In **batch F6, F7 & F8** design for dry granulation method to develop formula. All the dissolution give very poor effect. Also tablet produce by this method are very friable and prinking effect after coating.

Drug Y:

Batch **F6 to F8**, design for using Pregelatinised starch 1500 LM as a binder in different concentration. But it does not give satisfactory result. Among all Batch F8 give good drug release.

From above graph represent of different dissolution of various trial. From the all the trial only **F6 to F8** trial shows good drug release. AHD Y gives satisfactory drug release by Dry Granulation Method.

5.1.4. Formulation and development of AHD X by Wet Granulation and AHD Y by Dry Granulation (F9 to F11) by using different disintegrant concentration in Dry Granulation.

Figure 5.7: Composition of Core Tablet (F9 to F11)

INGRIDIENT	F9 (mg/tab)	F1 (mg/tab)	F11 (mg/tab)
INTRAGRANULER PART (WET GRANULATION)			
AHD X	40.000	40.000	40.000
Mannitol (Pearlitol 25C)	71.000	71.000	71.000
Lactose Monohydrate (Pharmatose 200M)	8.000	8.000	8.000
LHPC LH11	35.000	35.000	35.000
Vitamin E TPGS	2.000	2.000	2.000
Pregelatinised Starch (Lycatab PGS)	4.000	4.000	4.000
Purified Water	QS	QS	QS
Total	**160.000**	**160.000**	**160.000**
INTRAGRANULER PART (DRY GRANULATION)			
AHD Y	13.870	13.870	13.870
Microcrystalline Cellulose 112D	30.000	20.000	15.000
Mannitol (Pearlitol SD200)	44.130	44.130	44.130
LHPC LH11	5.000	15.000	20.000
Aerosil 200	4.000	4.000	4.000
Stearic Acid 95	2.000	2.000	2.000
Magnesium Stearate	1.000	1.000	1.000
Total	**260.000**	**260.000**	**260.000**
EXTRAGRANULER PART			
Mannitol (Pearlitol SD200)	29.000	29.000	29.000

Aerosil 200	4.000	4.000	4.000
Stearic Acid 95	5.000	5.000	5.000
Magnesium Stearate	2.000	2.000	2.000
Total	**300.000**	**300.000**	**300.000**

LHPC LH11= Low substituted Hydroxy Propyl Cellulose (LH-11)

Weigh all ingredient. AHD X, Mannitol (Pearlitol 25C), lactose monohydrate and Low substituted Hydroxy Propyl Cellulose (LH-11) shifted through 40# sieve. Mix all ingredients in polybag for 10 minutes. Transfer all material in Rotatory mixture granulator (RMG). Make 7% w/w pregelatinised starch solution by using hot water of 65 ~ 70° C. Vitamin E TPGS added into warm water. Mix ingredient in RMG by on chopper motor for 10 min. Add above solution gradually and start chopper on an appropriate rotation to break lumps. Stop impeller and chopper motor after completing addition. Granules passed through 1.413µm screen in Quadro® comill for uniform granules. Granules are transferred in rapid dryer for drying. Dry granules till LOD reduce up to 1.5 – 2.5 %w/w. Granules passed through 24# sieve.

Weigh all above AHD Y part interagranuler material accurately. Pass all material except magnesium stearate passed through 40# sieve. Magnesium stearate passed through 60# sieve. Mix all ingredient in polybag by hand mixing for 15 minutes. Material transfer to the roller compacter for making compacts. Collect compact & fines and separate it using 14# sieve. Compacts are transferred into QUADRO® co mill for milling. First all compacts are passed through 6.016mm screen at low speed for reducing time. These small compacts material again passed through 1.124mm sieve to convert them into granules. These granules are transferred into vibrating sieve shaker to shift them in 80# sieve. Retained material is collected as granules and passed material is collected as a fines. These fines are added to 14# passed fined producing in roller compacter. Repeat cycle until granules and fines ratio achieved up to 50:50.

Weigh all above extra granules material. Pass all material except magnesium stearate passed through 40# sieve. Magnesium stearate passed through 60# sieve. These are transferred into above granules. Mix them into polybag for 10- 15 min.

Compress tablet by using 9.00 mm round bevel shaped, plain bottom punch and upper punch embossed 930 in D tooling. Hardness of the tablets was maintained at 7-8 Kg/cm2 and tablet weight at 300 mg. Coat the tablet as described in previous batch.

Table 5.8: Post Compression Evaluation

Trial	Diameter (mm)	Thickness (mm)	Weight Variation (mg)	% Friability
F9	9.03	4.96±0.9	299 ± 1.7	0.432
F10	9.03	4.99±1.2	300 ± 1.4	0.342
F11	9.02	5.01 ±0.6	301 ± 1.7	0.412

Trial	Disintegration Time (min.sec)	Hardness (kp)	Drug Content (AHD X)	Drug Content (AHD Y)
F9	1.45	8.1 ± 0.03	98.64%	96.76%
F10	1.13	9.2 ± 0.03	99.87%	99.78%
F11	1.56	8.0 ± 0.01	97.55%	99.27%

In F9 batch, the Disintegration time is increase.Drug Content of both the drugs are optimum.

In F10 batch, here the Disintegration time, Hardness of tablet and Drug Content of both the drugs are optimum and as per the requirement. So it will be the optimised batch.*

In F11 batch, here Disintegration is not matching to the requirement.

Above all batches are also optimized on the basis of drug release data.

% Friability is less than 1% in above all batches. Which is optimum.

***** Innovator formulation: Disintegration Time-Around 1 min., Hardness- 7.5-9.5

5.1.4.1. *In-vitro* drug release of AHD X and AHD Y

Time (min)	Drug X			Drug Y		
	F9	F10	F11	F9	F10	F11
0	0	0	0	0	0	0
5	24.7	40.6	37.2	48.5	45.8	46.7
10	36.8	52.8	49.7	59.3	55.4	53.5
15	48.2	66.7	63.8	64.9	74.2	59.2
20	59.7	74.5	70.5	78.4	84.3	68.9
25	75.4	81.5	78.9	89.3	94.7	88.3
30	84.8	91.8	88.7	94.3	96.4	87.4
45	96.2	99.4	93.5	95.1	99.1	89.6

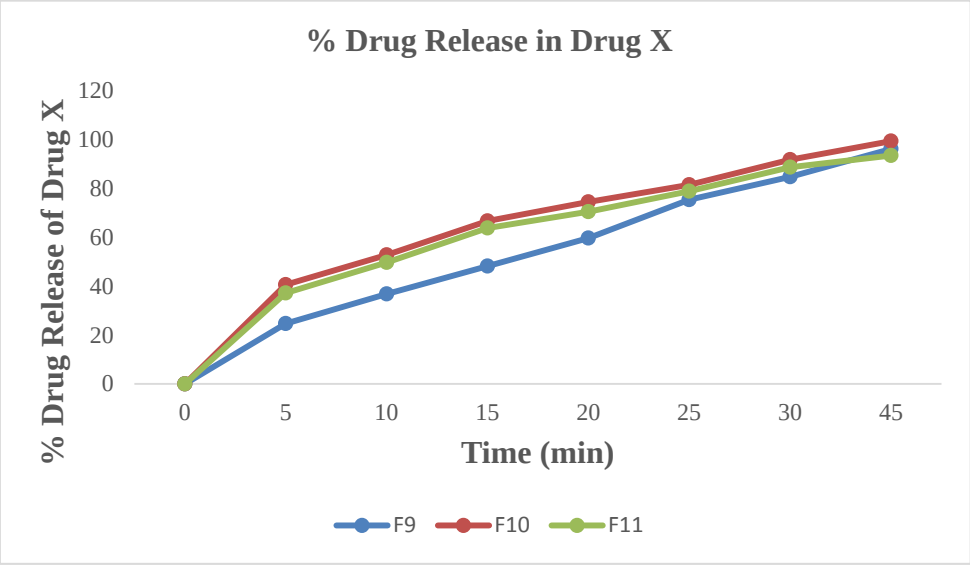


Figure 5.7: Drug Release of in 6.8 pH Phosphate Buffer Solution

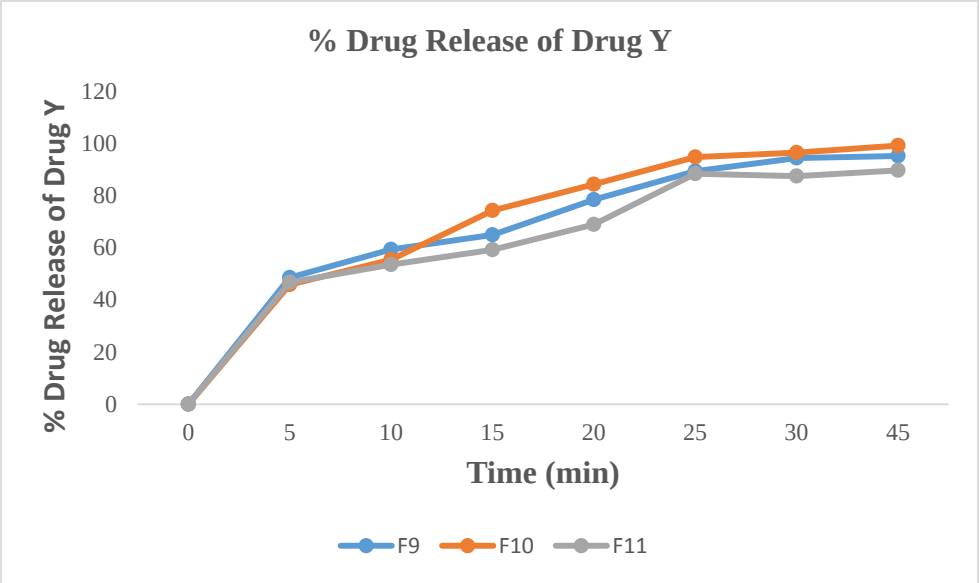


Figure 5.8: Drug Release of AHD Y in 6.8 pH Phosphate Buffer Solution

Drug X:

In **batch F9, F10 & F11** formulate to develop by using AHD X wet granulation and AHD Y by dry granulation. All the Precompression and postcompression parameter are given satisfactory result. Here, all batches were design to optimize different binder concentration in Dry Granulation part. From among all, F10 having satisfactory effect. **So F10 batch is optimized batch having satisfactory drug release.**

Drug Y:

In batch **F9 to F11**, LHPC LH 11 is used as a binder and give satisfactory drug release compare to previous trial. Among all F10 batch is very satisfactory result and 99.1% drug release of AHD Y**. So we concluded that F10 batch is optimized batch.** From above graph represent of different dissolution of various trial. From the all the trial only **F9 to F11** trial shows good drug release. AHD Y gives satisfactory drug release by Dry Granulation Method.

6. Summary

The aim of research work entitled as “Formulation Development and Evaluation of Immediate Release Fixed Dose Combination of Anti-hypertensive Agents” was to formulate fixed dose combination of AHD X and AHD Y immediate release drug delivery.

AHD X is an ARB that selectively inhibits the binding of angiotensin II to AT1, which is found in many tissues such as vascular smooth muscle and the adrenal glands. So it is used to reduce blood pressure. AHD Y is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the movement of calcium ions into vascular smooth muscle cells and cardiac muscle cells. AHD Y inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Both drug used in management of Hypertension.

AHD X having half-life is 13 hour and AHD Y having half-life is 20-30 hour. So combination of these drug produce satisfactory result. Initially UV Spectrophotometric analytical method was developed using 257 nm and 239 nm as λmax of AHD X and AHD Y in Phosphate buffer pH 6.8 respectively.

In the present study, an attempt was given to formulate immediate release drug delivery of AHD X and AHD Y in Combination using wet granulation and dry granulation technique. Literature review suggest that it is difficult to generate combination of drug in single unit as well as by wet granulation method.

AHD Y is hygroscopic drug that drastically degraded in presence of water so we perform coating on the tablet to prevent atmospheric moisture contact to AHD Y.

Various trial design to produce optimization of formula by using different approaches. Initially preliminary batches F1 & F2 are design using two different binder like Prgelatinised Starch and corn starch. Among both of them Pregelatinised starch gives satisfactory result compare to Corn starch, but result is still poor of two drug.

First enhancing drug release of AHD X by using different Solubilizing agent, to increase its solubility. Poloxamer 407, SLS and Vitamin E TPGS is used in three different trial F3, F4 and F5 respectively. Among them Vitamin E TPGS gives

satisfactory drug release of AHD X. It is also enhanced the drug release of AHD Y. But it does not achieve satisfactory result of AHD Y.

Another Dry granulation batch is design to increase dissolution of AHD Y in dosage form. Three different F6, F7 and F8 design having different binder concentration that gives enhance dissolution of AHD Y but gives poor drug release of AHD X. Among all F8 gives satisfactory drug release of AHD Y but poor drug release of AHD X.

So From above trial we consider two different granulation technique for different drug for enhancing drug release. AHD X shows good drug release by wet granulation technique and solubilizing agent Vitamin E TPGS. AHD Y gives satisfactory drug release by dry granulation technique. Extra granulating material are added to enhance flow property. So in batch F9 to F11, AHD X granules prepared by wet granulation method and AHD Y is prepared by Dry granulation technique. Among these trials, F10 gives satisfactory result of drug release of AHD X and AHD Y about 99%.

Part- II: Minor Project

"FORMULATION DEVELOPMENT AND EVALUATION OF IMMEDIATE RELEASE FIXED DOSE COMBINATION OF ANTI-HYPERTENSIVE PELLETS"

"FORMULATION DEVELOPMENT AND EVALUATION OF IMMEDIATE RELEASE FIXED DOSE COMBINATION OF ANTI-HYPERTENSIVE PELLETS"

The occurrence of hypertension is high in the patients with different of diseases like diabetes mellitus, chronic kidney disease and chronic cardiovascular disease. In addition, these subjects have the lowest control of blood pressure (BP) among the hypertensive patients and also the risk having a morbid or fatal cardiovascular event>20% in 10 years. For these reasons, the aggressive control of BP to <130/80 mm Hg for these subjects is strongly recommended by National and International guidelines. Oral drug delivery is the most preferred route for the various drug molecules among all other routes of drug delivery, because ease of administration which lead to better patient compliance. So, oral immediate release drug delivery system becomes a very promising approach for those drugs that are given orally but having the shorter half-life and high dosing frequency. To achieve this goal, Pelletization is a most convenient method. At present time pharmaceutical research and development showing its interest on drug delivery which enhances therapeutic action while minimizing side effect. It will decrease risk of dose dumping, flexibility of blending to attain different release pattern as well as reproducible and short gastric residence time. Pelletization is a novel approach for the formation of spherical beads or pellets which converts the fine powder into pellets. Different novel techniques for pelletization such as cryopelletization, freeze pelletization, Hot melt extrusion and melt spheronization along with traditional techniques, thus extending the frontier of future pharmaceutical development. Here, the combination of class I and class II drugs are formulated and developed. Here the different ratios of diluent, binder, superdisintegrant and solvent were optimized. Formulated pellets were evaluated for % friability, aspect ratio, %yield, disintegration time, sphericity, drug content, in vitro drug release.

1. Aim of Present Investigation

- To prepare immediate release fixed dose combination of Anti-hypertensive agents.
- It should have quick on set of action.
- To prepare the formulation which reduce the chances of dose dumping and having no side effects.
- To prepare stable form of drugs.
- To reduce dosing frequency of drugs.
- To reduce the toxicity.
- To develop the formulation which improve the ability to provide special effects
- To prepare formulation which improve treatment efficacy.
- To protect the drug from being hydrolysis and degradation.
- To prepare formulation which minimize the chances of accumulation with the chronic dosing.
- To prepare the formulation which maximizing absorption.
- To develop the formulation which reduces inter and intra-patient variability.

2. Introduction

2.1. Pelletization[33,34]

Pelletization is an agglomeration procedure that proselytes fine powders or granules of mass medications and excipients into little, free streaming, round or semi circular units, alluded to as pellets. Pellets range in size, regularly, between 0.5 – 1.5 mm, however different sizes could be readied. Pellets can be set up by numerous strategies, the compaction and medication layering procedures being the most broadly utilized today. Notwithstanding which producing procedure is utilized, pellets need to meet the accompanying prerequisites.

(1) They ought to be close circular and have a smooth surface; both considered ideal qualities for resulting film covering.

(2) The molecule size extent ought to be as restricted as could be expected under the circumstances. The ideal size of pellets for pharmaceutical use is thought to be somewhere around 600 and 1000 μm.

(3) The pellets ought to contain however much as could be expected of the dynamic fixing to keep the extent of the last dose structure inside sensible points of confinement.

Pellets are for pharmaceutical purposes and are created fundamentally with the end goal of oral controlled delivery, solid shapes having gastro safe or controlled delivery properties or the capacity of site-particular medication conveyance. For such purposes, covered pellets are controlled as hard gelatin cases or deteriorating tablets that rapidly free their substance of pellets in the stomach. As medication conveyance frameworks turn out to be more advanced, the part of pellets in the outline and improvement of measurements structures is expanding. Detailing of medications in numerous unit compacted into tablets, offers adaptability as to target release properties. The wellbeing and viability of the plan is higher than that of other measurement frames.

Pellets give high level of adaptability amid the outline and improvement of oral measurement shapes. They can be partitioned into fancied dosage qualities without

definition or procedure changes, and can likewise be mixed to convey inconsistent bioactive specialists at the same time or particles with different release profiles at the same site or at various locales inside the gastrointestinal tract.

Likewise, pellets have various helpful points of interest over customary single units, for example, tablets and powder filled cases. Taken orally, pellets for the most part scatter unreservedly in the gastrointestinal tract, and subsequently expand the medication retention, minimize nearby aggravation of the mucosa by certain aggravation drugs as a result of the little amount of medication accessible in a solitary pellet, and lessen bury and intrapatient variability.

As the upsides of pellets over single units turned out to be clear, the pharmaceutical business all in all began to dedicate assets to lead research in pellet innovation and, at whatever point conceivable, obtain propelled gear appropriate for the production of pellets.

Pellets might be made by utilizing diverse techniques as indicated by the application and the decision of maker. The techniques utilized for Pelletization are basically the same as the granulation strategies. The most broadly utilized procedures are expulsion and spheronization and arrangement or suspension layering, and powder layering. Different procedures with restricted application in the advancement of pharmaceutical pelletized items incorporate globulation, balling, and pressure.

2.1.1. Advantages of Pellets[33,35]:

- They can be partitioned into coveted measurement quality without procedure or plan changes.
- When pellets containing the dynamic fixing are as suspension, cases, or breaking down tablets, they offer noteworthy restorative points of interest over single unit dose shapes.
- They can likewise be mixed to convey contradictory bioactive specialists.
- They can likewise be utilized to give diverse discharge profile at the same or distinctive destinations in the gastrointestinal tract.

- Pellets offer high level of adaptability in the configuration and improvement of oral dose structure like suspension, sachet, tablet and case
- Pellets scatter openly in gastro intestinal tract (GIT),maximize drug retention, and minimize local irritation of the mucosa by certain aggravation drugs.

- **Improved stream attributes:** Spheres have excellent stream properties, which can be utilized in automated forms or as a part of procedures where exact dosing is required, e.g. tableting, forming operations, capsule filling, and bundling.
- **Coating:** Coating of granules is frequently connected for stabilizing dynamic fixings in the granule or to control the arrival of these dynamic fixings. Typical applications in the pharmaceutical business are the controlled discharge medications. The simplest shape to coatis the circle because of the nonattendance of edges. It is additionally the most sparing one to coat as no additional coating material is required to fill anomalies in the surface of the granules.
- **Packing of informal lodging:** In certain processes, porous beds or sections are utilized as concoction reactors. Spherical particles permit the multiplication of beds with always the same void volume, surface region and permeability. Counts and expectations of the process qualities likewise get to be less demanding when round particles are utilized the same number of conditions are based onflows around symmetrical bodies.
- **Density build:** Both the genuine and the mass thickness of granules are expanded by spheronising. This can improve the procedure and the bundling.
- **Marketing:** For buyer items, spheronising is sometimes connected for enhanced product appearance and advertising reasons.
- **Hardness and friability:** Hardness and friability depend on the inside strong powers and surface characteristics. Spheronization expands the hardness and decreases the friability of granules. This will reduce the measure of fines created amid taking care of or transportation.

2.1.2. Disadvantages of Pellets[33,35]:

- Dosing by volume instead of number and splitting into single measurement units as required.
- Involves case filling which can increment the costs or tableting which annihilate film coatings on the pellets.
- The size of pellets fluctuates from plan to formulation however more often than not lies between 1 to 2 mm.

2.1.3. Desirable Properties of Pellets[33]:

➢ **Uncoated pellets:**

- Uniform spherical shape,
- Uniform size,
- Good flow properties,
- Reproducible packing,
- High strength,
- Low friability, Low dust,
- Smooth surface,
- Ease of coating.

➢ **Once coated:**

- Maintain all of the above properties,
- Have desired drug release characteristics.

2.1.4. Methods of Pelletization[33,36,37]

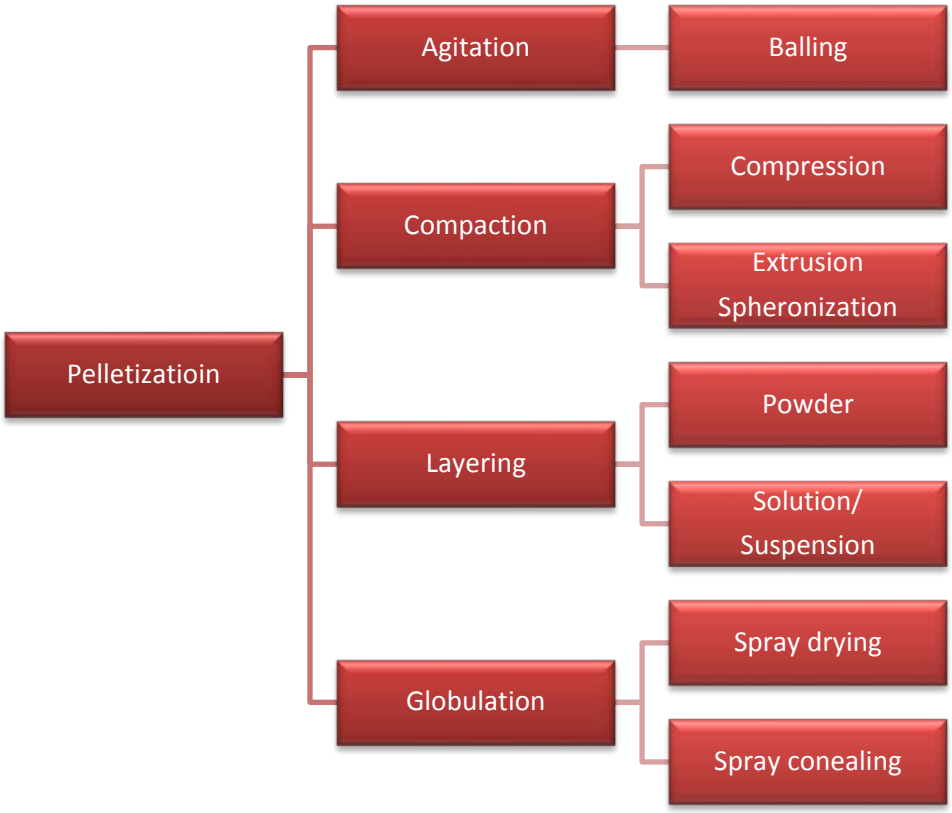


Figure 2.1: Techniques of Pelletization

2.1.4.1. Pellet Formation and Growth[33]:

Contingent upon the sort of hardware and procedure chose for pellet arrangement and development may happen in various ways. The accompanying techniques portray the deliberate development of pellets amid the different pelletization forms as far as the holding strengths and the basic development systems.

i) Balling

This method is not well known in the pharmaceutical business as a pelletization procedure, presumably because of the requirements of molecule size conveyance and substance consistency. Work around there is required to proceed. It is fitting, along these lines, to analyze the different periods of pellet development in a drum,

container, or plate pelletizer. The principal stage, known as the nucleation district, includes the irregular impact and resulting blend of the essential particles to give very much framed cores. The sizes of the cores rely on upon the sizes of the essential particles, the dampness content, the thickness of the coupling fluid, and the wettability of the substance. Taken after by the transition region where particles crash into each other and coalescein a special liquid, or where littler particles are crushed and layered on vast particles. This system inthis area is, hence, estimate subordinate; fines that are delivered through wearing down or pulverizing are grabbed by substantial pellets. Creation of fines and consequent blend and layering proceeds until a period is achieved when the quantity of good impacts decreases quickly, along these lines prompting a diminishment in the rate of development of the pellets. Now, the third stage, known as the ball development area, is come to. In this district surface scraped spot gets to be set apart; accordingly, layering turns into the prevalent system of development i.e., round agglomeration or emulsion dissolvable dissemination. Amid the procedure, the tumbling activity in the pelletizers permits the particles to re-orientate themselves and structure thick pellets of considerable quality. The strength of the uncured pellets is straightforwardly identified with the surface pressure of the coupling fluid which thus influences the suction potential that forms into the pellets.

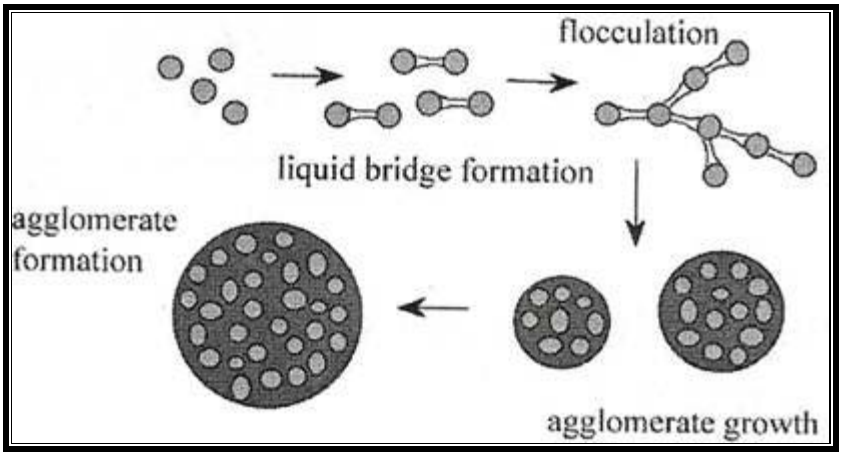


Figure 2.2: Pellet growth mechanisms- (spherical agglomeration)

ii) Compaction (Extrusion-Spheronization)

Compaction is a type of weight agglomeration, in which sedate particles or granules are constrained together with or without detailing helps by a mechanical power to produce pellets of very much characterized shapes and sizes. The pelletization procedure can be subdivided into pressure and expulsion. In the primary phase of pressure, particles that are pre-treated through the mixing or wet granulation took after by drying, revises themselves to shape a firmly stuffed mass, amid this procedure, particles hold the majority of their properties.

At high weights, expanded inter particle contact is observed. Mechanical interlocking is the main holding system that does not include any powers and is required to contribute almost no to the physical quality of the pellet. On cooling, the liquid material structures extremely solid strong extensions, tapped dampness, though irrelevant may likewise add to holding through fine forces. In the second stage, the granulation is then put into the extruder to deliver high-thickness extrudates. These extrudates are reinforced together by fine powers, strong extensions framed because of loss of dampness, mechanical interlocking and to some degree, atomic powers. These extrudates are at long last changed over to pellets on spheronization. Amid the procedure, the dampness is constrained out from the pellet inside into the outside and gives pliancy to the pellet surface. The surface versatility, combined with the simultaneous tumbling of the particles in the spheronizer, permits the development of round pellets.

iii) Globulation

It is a procedure where hot melts, arrangements, or suspensions are atomized to create circular particles or pellets. In globulation, atomization produces strong particles straightforwardly from the fluid stage through dissipation or cooling and consequent cementing of hot melts, arrangement and suspension. Amid shower drying, the atomized beads are reached by a hot gas stream and dissipation of the fluid is started, which includes synchronous warmth and mass exchange and relies on upon the temperature, moistness, and transport properties of the air encompassing the bead. As more fluid vanishes, surface immersion conditions are come to and arrangement of strong starts. These particles are at first held together by fine strengths created by the

fluid stage and are bit by bit supplanted by strong extensions. Continuation of the procedure prompts the arrangement of a permeable layer or outside layer on the surface of the beads and thickness of the covering increments through both dissipation and ensuing crystallization of the disintegrated material that may incorporate dynamic medication, solidifying fastener or any different excipients which have solvency in the coupling fluid. The rate controlling component is the dispersion of the fluid through the extending outside layer, trailed by convective transport from the surface of the shell. In crosslinking strategy, the polymer is rigidized by synthetic response with the cross connecting specialists, for example, aldehydes, calcium chloride, and so on.

During spray congealing, the atomized droplets were cooled below the melting point of the vehicle. The particles were held together by solid bonds formed from the congealed melts. Due to the absence of solvent evaporation during most spray congealing processes, the particles were generally nonporous and strong and remain intact upon agitation. The processing conditions play a very significant role in the development of good quality pellets, it is the physical forces that first bond the primary particles together and initiate the pelletization process. The propensity and strength of these physical forces depend to a large extend, upon the physicochemical properties of the formulation components. Therefore the physical forces coupled with the elementary growth mechanisms ultimately determine the strength and performance of pellets and should be taken into account during the design and development of pellet dosage forms.

3. Literature Review of Dosage Form

Vishal Sachdeva et al[34] examined that Oral medication conveyance is the most favored course for the different medication particles among all different courses of medication conveyance, since simplicity of organization which prompt better patient consistence. Thus, oral developed discharge drug conveyance framework turns into an extremely encouraging methodology for those medications that are given orally yet having the shorter half-life and high dosing recurrence. Late patterns demonstrate that multiparticulate drug conveyance frameworks are particularly reasonable for accomplishing expanded discharge oral details with okay of measurements dumping, adaptability of mixing to achieve distinctive discharge designs and additionally reproducible and short gastric home time. The arrival of medication from pellets relies on upon an assortment of components including the transporter used to shape pellets and the measure of medication contained in them. Subsequently, pellets give gigantic chances to planning new controlled and amplified discharge oral definitions, therefore amplifying the wilderness of future pharmaceutical improvement.

Harshal Gavali et al[35] studied that Multiparticulates are discrete particles that make a different unit framework. In pharmaceutical industry pellets can be characterized as little, free streaming, circular particulate produced through the group of fine powder or granules of medication substances and excipients utilizing fitting taking care of gear. A present survey plots the transient record of terrifically critical assembling and assessment method of pellets. The assembling systems are as spheronization and exctrusion, pelletization by arrangement layering, hot-melt exctrusion, cryopelletization, solidify pelletization have been pondered.

J Paul et al[38] studied that changed starch (high-amylose, crystalline and safe starch) as the primary excipient for quick discharge pellets containing inadequately dissolvable medications (hydrochlorothiazide and piroxicam) and arranged by means of expulsion/spheronisation. The bioavailability of pellets (containing 50 mg hydrochlorothiazide) was resolved after oral organization to 6 canines. A 24-factorial outline with essential issue was utilized to assess the impact of hydrochlorothiazide (10% and half, w/w), HPMC (folio, 4% and 7%,w/w), sorbitol (0% and 10%, w/w)

and water (granulation fluid, low and abnormal state) on pellet yield, size (Feret mean breadth) and sphericity (viewpoint proportion and two-dimensional shape component, eR). Ideal granulation fluid substance relied on upon medication and sorbitol level in the detailing. All elements aside from sorbitol content, and additionally the connections between medication focus and folio level and amongst medication and water level, were huge ($P < 0.05$) for pellet yield, while a critical ebb and flow ($P < 0.05$) recommended non-linearity of the reaction plots. The model was not huge for pellet shape, while hydrochlorothiazide and water level and their cooperation were noteworthy ($P < 0.05$) for pellet size. Pellet friability, breaking down, remaining water content and in-vitro drug discharge were resolved. Pellets containing 2.5% (w/w) piroxicam were likewise assessed. For both model medications, pellets with a high return (>90%), adequate sphericity (AR < 1.2) and low friability (<0.01%) were acquired. Because of pellet deterioration, quick disintegration of both hydrochlorothiazide and piroxicam was accomplished: >80% drug discharged in 30 min. The bioavailability (AUC0fi24 h, Cmax and tmax) of hydrochlorothiazide pellets in puppies was not fundamentally unique in relation to quick breaking down prompt discharge hydrochlorothiazide tablets ($P > 0.05$).

V.S. Nair et al[39] concentrates on demonstrates that pharmaceutical innovative work demonstrating its enthusiasm on medication conveyance which improves restorative activity while minimizing reaction. Utilization of multi-particulate is the endowment of that examination which accomplishes postponed or controlled discharge with generally safe of dosage dumping, adaptability of mixing to achieve diverse discharge design and reproducible and short gastric living arrangement time. Pelletization is a novel methodology for the arrangement of circular dots or pellets from fine powder or mix so as to create site particular medication conveyance framework. Distinctive methods of pelletization, for example, suspension/arrangement layering, expulsion and spheronisation, cryopelletization and so on can be utilized for the development of multi particulate medication conveyance framework. Keeping in mind the end goal to give augmented or deferred discharge definition, accordingly broadening the boondocks of future pharmaceutical advancement.

4. Experimental Work

4.1. Methods

4.1.1. Preparation of IR Pellets of AHD X & AHD Y:

Procedure:

Drug X and Drug Y were mixed with MCC 102 (30-70%), Lactose Monohydrate (Q.S.), Crosscarmelose sodium (5-15%), PVP K30 (5-10%). The powders were dry mixed for 5 min. in mortar piston. The batch size was 15 g of dry material. The mixture was wetted with purified water (33 - 60% of the total mass) using mortar piston.

Here, the concentration of MCC and Lactose Monohydrate were optimized by taking the different ratios of MCC and Lactose Monohydrate. Amount of solvent (water) also optimized by adding different volume of solvent. Then the concentration of binder PVP K30 was optimized and after it, concentration of Superdisintegrant Crosscarmelose Sodium was optimized which affects on disintegration time and drug release of pellets. In pelletization next steps were extrusion, spheronization and drying of pellets.

- **Extrusion**

The wet mass was extruded at an extrusion speed of 150 rpm by means of a gravity fed

extruder. (sieve size-1mm)

- **Spheronization**

The extrudates were spheronized at 3500 rpm for 5 min. and then 6000 rpm for 20 min. in a spheronizer using a friction plate with cross-hatched geometry.

- **Drying**

The pellets were dried in aoven at 50°C for 10 min.

4.1. Evaluation of Pellets:

- **Determination of the Size and Size Distribution:**

Size analysis of pellets was carried out by sieve analysis using a nest of sieves containing mesh 10 # to 100 #. Total pellets collected in each batch were used and shaking time was kept 5 min. The pellets retained on each sieve were weighed. The pellets were assigned the mesh number of the screen through which it passed or on which it was retained. It was expressed in terms of arithmetic mean of the two sieves. Mean particle size of the pellet was calculated using following formula:

Mean particle size (µm) = ΣXiFi * ΣFi …..Eq 4.1

Where,

ΣXiFi = Weight size,

ΣFi = Percent weight size

The pellet yield was calculated based on the pellet fraction retained on sieve 20 # and presented as a percentage of the total pellet weight.

- **Aspect Ratio:**

Aspect ratio or elongation measures the oblongation of the particles. Aspect ratio decreases with higher sphericity. At least 50 pellets from each batch were randomly selected for measurement of aspect ratio. The maximum and minimum diameters of the pellets were measured using digital micrometer. Aspect ratio was measured using following formula:

Aspect Ratio $= \frac{dmax}{dmin}$ …..Eq 4.2

Where,

dmax= Maximum diameter of the pellets

dmin= Minimum diameter of the pellets

- **Friability :**

6 gm accurately weighed pellets were taken and placed in Roche friabilator. The test apparatus was rotated at 25 rpm for 4 minutes. 25 stainless steel balls (diameter 4 mm, weighing 0.250 g each) were used as attrition agents. After friability testing, the pellets were sieved through sieve no. 40 to remove fines generated. The weight loss (%F)after friability testing was calculated as:

$$\% F = \frac{W1-W2}{W1} \times 100 \quad \text{.....Eq 4.3}$$

Where,

W1= Initial weight of the pellets,

W2 = Weight of pellets after friability

Percentage friability less than 1% would be acceptable.

- **In Vitro dissolution studies:**

The dissolution study of capsule dosage forms containing pellets were performed in a USP dissolution apparatus-II (paddle apparatus). The dissolution medium consisted of 500 ml of 6.8 pH phosphate buffer in dissolution study. The dissolution study was carried out at 37 ± 0.5 ºC with speed of 50 rpm. The samples (5ml) were withdrawn at 5 min, 10 min, 15 min, 20 min, 25 min, 30 min and 45 min and 5 ml of fresh dissolution medium was added to the jar to keep constant volume to maintain sink condition. The samples were filtered by the wattman filter paper and drug absorbance was determined by using UV spectrophotometer at 257 nm for drug x and 239 nm for drug Y. From the calibration curve concentration of drug in each sample was determined.

5. Result & Discussion:

5.1. Optimization of Amount of Diluent (MCC) and Solvent

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
AHD X	13.3%			13.3%			13.3%		
AHD Y	3.3%			3.3%			3.3%		
MCC 102	30%			50%			70%		
Lactose Monohytrate	Q.S.			Q.S.			Q.S.		
PVP K30	3%			3%			3%		
CCS	10%			10%			10%		
Water	5ml	7ml	9ml	5ml	7ml	9ml	5ml	7ml	9ml

Table 5.1: Evaluation Data of Batches F1 to F9

Sr. No.	Batches	Solvent	Extrudes	Fines	Shape	% Yield	D.T. (min)
1	**F1**	W5	Very Good	+	Dumbbell	---	---
2	**F2**	W7	Very Good	+	Spherical	92.8	1.36
3	**F3**	W9	Lump	+++	Uneven & Brittal	---	---
4	**F4**	W5	Good	++	Dumbbell	---	---
5	**F5**	W7	Good	+	Dumbbell	---	---
6	**F6**	W9	Lump	+++	Uneven	---	---
7	**F7**	W5	Poor	+++	Dumbbell	---	---
8	**F8**	W7	Good	++	Dumbbell	---	---
9	**F9**	W9	Very Poor	+++	Dumbbell	---	---

Table 5.2: Evaluation Data of Batches F1 & F2

Batches	% Friability	Aspect Ratio	Drug Content of Drug X	Drug Content of Drug Y
F2	0.0589	1.022	98.36	95.86

From the observation it was revealed that as the concentration of the diluent decreased, it gave good extrudes and good sphericity to the pellets. **Batch F2** containing 30%w/w MCC 102 produced extrudes with the desired property and desired sphericity of pellets. As the amount of diluent increased, dumbbell formation was observed in the pellets and as the amount of diluent decreased, extrudes and pellets with desired property were obtained.

From the observation it was revealed that as the amount of the solvent increased, it gave good extrudes and good sphericity to the pellets with 30% of MCC. **Batch F2** containing 46.6 %w/v water produced extrudes with the desired property and desired sphericity of pellets. As the amount of solvent increased, lump formation was observed in the extrudes and as the amount of solvent decreased, extrudes and pellets with desired property were not obtained.

5.1.1. *In-vitro* drug release of AHD X & AHD Y

Time (min)	**Drug X**	**Drug Y**
	F2	**F2**
0	0	0
5	31.2	27.8
10	41.6	43.1
15	56.7	54.4
20	69.8	64.7
25	78.7	78.5
30	91.3	88.4
45	99.3	97.4

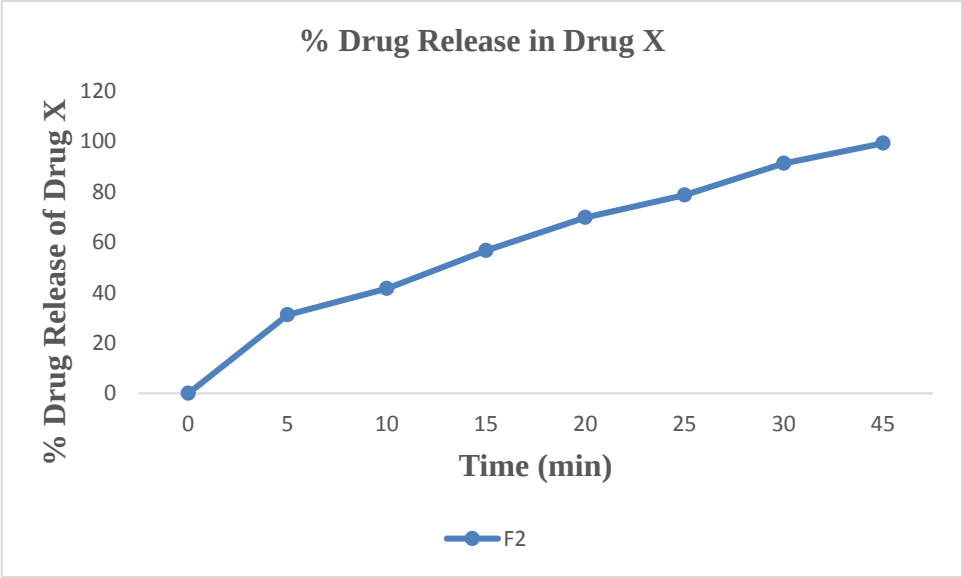


Figure 5.1: Drug Release of AHD X

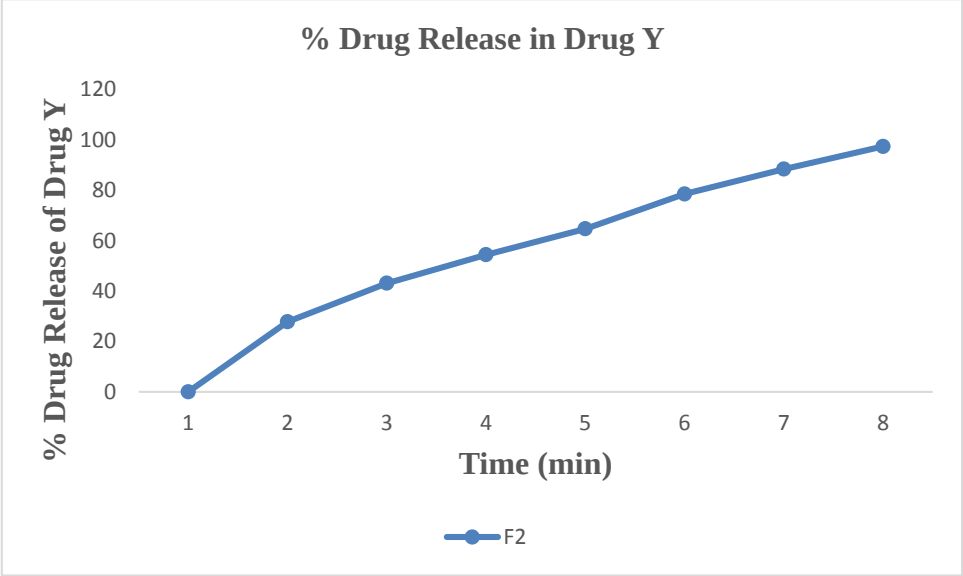


Figure 5.2: Drug Release of AHD Y

5.2. Optimization of Concentration of Binder

Ingredients	F10	F11	F12
AHD X	13.3%	13.3%	13.3%
AHD Y	3.3%	3.3%	3.3%
MCC 102	30%	30%	30%
Lactose Monohydrate	Q.S.	Q.S.	Q.S.
CCS	10%	10%	10%
Water	7ml	7ml	7ml
PVP K30	1%	2.5%	5%

Table 5.3: Evaluation Data of Batches F10 to F12

Sr. No.	Batches	Extrudes	Fines	Shape	% YIELD	D.T. (min)
1	F10	Good	+	Dumbbell	---	---
2	F11	Very Good	-	Spherical	93.8	1.29
3	F12	Very Good	-	Spherical	97.5	2.02

Table 5.4: Evaluation Data of Batches F11 & F12

Batches	% Friability	Aspect Ratio	Drug Content of Drug X	Drug Content of Drug Y
F11	0.0582	1.131	98.27	97.86
F12	0.0463	1.075	95.04	97.24

In the above trials 1 to 5 % w/w of PVP k30 was used. Batch **F11**containing MCC as diluent and 2.5 %w/w PVP k30 produced extrudes and pellets as desired. Amount of fines and friability decreased due to incorporation of binder. As Batch **F11** gave good sphericity of pellets compared to Batch 10, where Batch **F12** produced extrudes and pellets as desired but disintegration time was not as per require.

5.2.1. *In-vitro* drug release of AHD X & AHD Y

Time (min)	**Drug X**		**Drug Y**	
	F11	**F12**	**F11**	**F12**
0	0	0	0	0
5	33.4	21.2	30.2	16.4
10	46.5	31.7	48.2	30.8
15	59.2	52.3	59.7	39.7
20	71.3	58.9	69.3	54.7
25	82.9	64.1	79.5	64.3
30	93.6	73.8	90.2	71.3
45	98.9	82.4	98.7	84.7

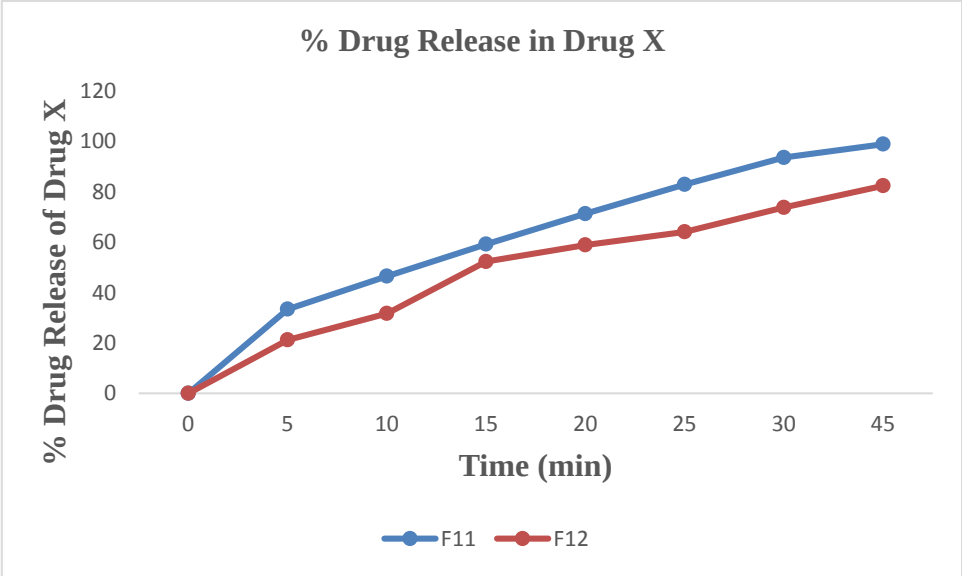


Figure 5.3: Drug Release of AHD X

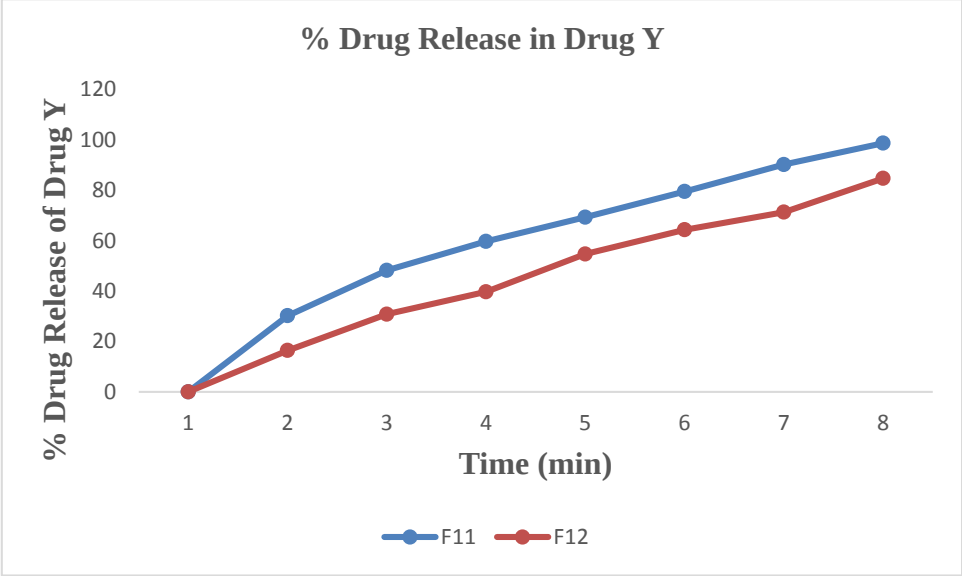


Figure 5.4: Drug Release of AHD Y

5.3. Optimization of Concentration of Disintegrant

Ingredients	F13	F14	F15	F16
AHD X	13.3%	13.3%	13.3%	13.3%
AHD Y	3.3%	3.3%	3.3%	3.3%
MCC 102	30%	30%	30%	30%
PVP K30	2.5%	2.5%	2.5%	2.5%
Lactose Monohydrate	Q.S.	Q.S.	Q.S.	Q.S.
Water	7ml	7ml	7ml	7ml
CCS	5%	7.5%	10%	15%

Table 5.5: Evaluation Data of Batches F13 to F16

Sr. No.	Batches	Extrudes	Fines	Shape	% Yield	D.T. (Min.)
1	**F13**	Good	-	Dumbbell	---	---
2	**F14**	Very Good	-	Spherical	91.4	2.54
3	**F15**	Very Good	-	Spherical	92.8	1.28
4	**F16**	Poor	+++	Uneven & Brittal	---	---

Table 5.6: Evaluation Data of Batches F14 & F15

Batches	% Friability	Aspect Ratio	Drug Content of Drug X	Drug Content of Drug Y
F14	0.0563	1.055	96.69	98.73
F15	0.0598	1.032	98.55	97.86

From the observation it was revealed that as the amount of the superdisintegrant decreased, it gave good extrudes and good sphericity to the pellets. **Batch F14 and F15** containing 46.6 %w/v water produced extrudes with the desired property and desired sphericity of pellets. As the amount of superdisintegrant increased, uneven and brittal formation was observed in the pellets and as the amount of superdisintegrant decreased, extrudes and pellets with desired property were not obtained.

5.3.1. *In-vitro* drug release of AHD X & AHD Y

Time (min)	Drug X		Drug Y	
	F14	**F15**	**F14**	**F15**
0	0	0	0	0
5	26.8	31.5	23.1	29.7
10	35	44.3	35.3	46.4
15	58.2	57.4	52.3	63.1
20	64	73.2	66	71.8
25	73.2	81.5	76.2	82.4
30	83.5	93.1	87.4	93.4
45	94.1	99.2	95.1	99.2

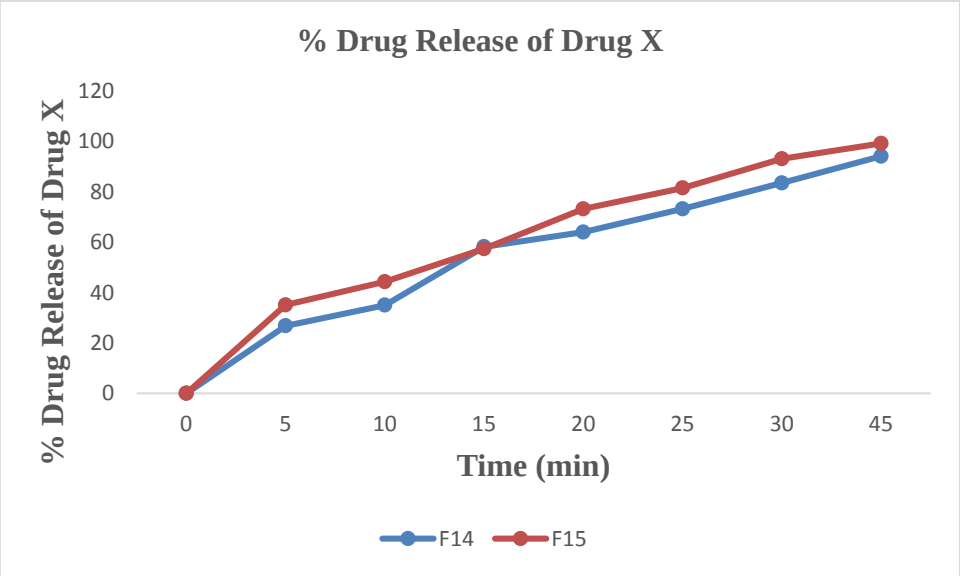


Figure 5.5: Drug Release of AHD X

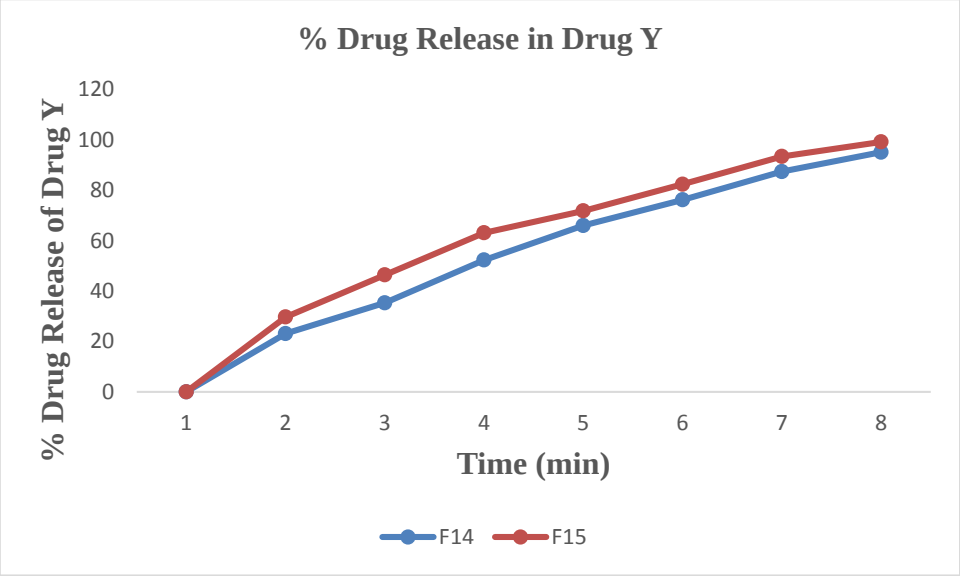
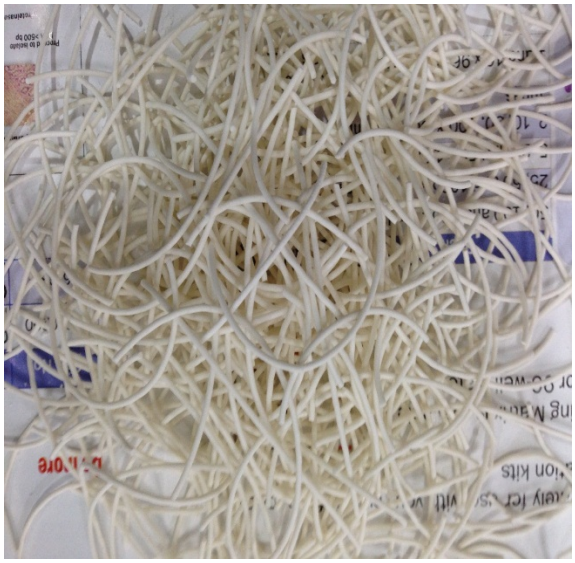
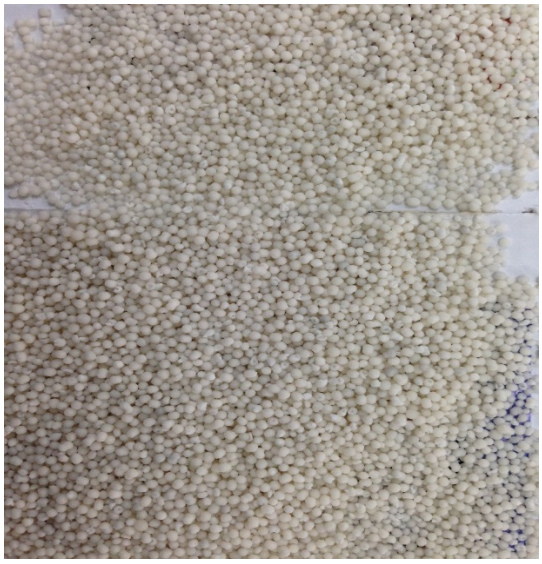


Figure 5.6: Drug Release of AHD Y



Extrude



Uneven & Brittal Shape

Dumbbell Shape

Spherical Shape

6. Summary

Here, the combination of class I and class II drugs are formulated and developed. Different ratios of diluent, binder, superdisintegrant and solvent were optimized.

Batch F2 containing 30%w/w MCC 102 produced extrudes with the desired property and desired sphericity of pellets. As the amount of diluent increased, dumbbell formation was observed in the pellets and as the amount of diluent decreased, extrudes and pellets with desired property were obtained.

From the observation it was revealed that as the amount of the solvent increased, it gave good extrudes and good sphericity to the pellets with 30% of MCC. **Batch F2** containing 46.6 %w/v water produced extrudes with the desired property and desired sphericity of pellets compare to other batches. As the amount of solvent increased, lump formation was observed in the extrudes and as the amount of solvent decreased, extrudes and pellets with desired property were not obtained.

In the above trials 1 to 5 % w/w of PVP k30 was used. Batch **F11**containing MCC as diluent and 2.5 %w/w PVP k30 produced extrudes and pellets as desired. Amount of fines and friability decreased due to incorporation of binder. As Batch **F11**gave good sphericity of pellets compared to Batch 10, where Batch **F12** produced extrudes and pellets as desired but disintegration time was not as per require.

From the observation it was revealed that as the amount of the superdisintegrant decreased, it gave good extrudes and good sphericity to the pellets. **Batch F14 and F15** containing 46.6 %w/v water produced extrudes with the desired property and desired sphericity of pellets. As the amount of superdisintegrant increased, uneven and brittal formation was observed in the pellets and as the amount of superdisintegrant decreased, extrudes and pellets with desired property were not obtained.

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