FORMULATION, EVALUATION AND OPTIMIZATION OF

AMLODIPINE IP 5MG FILM COATED TABLETS

A Dissertation submitted to

THE TAMIL NADU Dr.M.G.R.MEDICAL UNIVERSITY

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In partial fulfillment of the requirements for the award of the Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

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DECLARATION

I hereby declare with immense pleasure and satisfaction that this dissertation work entitled "**Formulation, Evaluation and Optimization of Amlodipine IP 5MG film coated tablets"** was carried out by me under the guidance of **Mr.Barish, M.Pharm, Ph.D (Institutional guide)**,Department of Pharmaceutics , R.V.S College of Pharmaceutical Sciences, Sulur, Coimbatore. and **Mr. Santhosh (Industrial guide)** Production Manager, Kerala State Drug and Pharmaceutical Limited, Kalavoor, Alappuzha, Kerala.

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<u>CERTIFICATE</u>

This is to certify that the research project work entitled **"Formulation , evaluation and optimization of Amlodipine IP 5 MG Film Coated Tablets"** is a bonafide genuine work carried on by **Mrs.REMYA.M (Reg.No: 261410762)** in partial fulfillment of the requirements for the award of degree in **Master of Pharmacy in Pharmaceutics** of **The Tanilnadu Dr.M.G.R.Medical University, Chennai,** in Kerala State Drug And Pharmaceuticals Limited, Alappuzha under my guidance and supervision to my fullest satisfaction.

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TO WHOMSOEVER IT MAY CONCERN

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She has put in her sincere efforts in completing the project work.

Her Character and Conduct is good during the period.

Junior Manager (P & A)

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This is to certify that the research project work entitled **"Formulation, Evaluation and Optimization of Amlodipine IP 5MG Film Coated Tablets "** is a bonafide genuine work carried out by **Mrs. REMYA.M (Reg.No. 261410762**) in partial fulfillment of the requirements for the award of degree in **Master of Pharmacy in Pharmaceutics** of **The Tamilnadu Dr.M.G.R Medical University, Chennai** at RVS College of Pharmaceutical Sciences and in the Production department of Kerala State Drug And Pharmaceutical Limited, Alappuzha under the guidance and supervision of **Mr.Barish,M.Pharm,Ph.D(Institutional guide)** Professor ,Department of pharmaceutics, R.V.S College of Pharmaceutical Sciences and **Mr.Santhosh (Industrial guide)** Production Manager, Kerala State Drug and Pharmaceutical Limited, Alappuzha.

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Evaluation Certificate

Dissertation work	:	**Formulation , Evaluation and Optimization of Amlodipine IP 5MG film coated tablets.**

Name of the Candidate	:	**REMYA.M (Reg No:261410762)**
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INTERNAL EXAMINER   **EXTERNAL EXAMINER**

Date:

Place:

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LIST OF ABBREVATIONS

S.NO	Abbreviation used	Meaning
1	ICH	International conference on harmonization
2	API	Active pharmaceutical ingredient
3	HPLC	High performance liquid chromatography
4	FT-IR	Fourier transform infrared spectroscopy
5	p^H	Hydrogen ion concentration
6	BCS	Biological classification
7	LOD	Loss on drying
8	NLT	Not less than
9	NMT	Not more than
12	BD	Bulk density
13	TD	Tapped density
14	CI	Compressibility index
15	HR	Hausner's ratio
16	RH	Relative humidity
17	RPM	Rotations per minute
18	µg	Micrograms
19	g	Gram
20	mg	Milligram
21	kg	kilogram
22	mm	millimeter
23	mmHg	Millimeter mercury
24	nm	nanometer
22	^0C	Degree centigrade
23	Std	Standard
24	MCG	Mixer com granulator
25	cm^2	Centimeter square
26	%	Percentage

ABSTRACT

The basic aim of of this study is the formulation, evaluation and optimization of immediate release amlodipine tablet IP 5mg film coated tablets by wet granulation method. Amlodipine is used in the treatment of mild to moderate hypertension, chronic stable angina pectoris or vasopastic angina (prinz metals or variant).Totally 9 preparations are prepared with Amlodipine.Sodium starch glycolate,Starch used as disintegrants,Magnesium stearate(lubricant). The amlodipine granules prepared separately in a rapid mixer granulator.Pre compression parameters like bulk density, true density, angle of repose, Compressibility index, Hausner's ratio indicate all the formulations are showing good flow properties. Granules are compressed to produce tablets are evaluated for post compression parameters like Wight variations, hardness, friability, disintegration and dissolutions parameters. In vitro dissolution profile of all the nine formulations compared with Innovator dissolution profile, from that F1-F6 does not show remarkable Dissolution profile with innovator dissolution profile. F7-F9 shows the 75-95% of drug release and match with innovator dissolution profile. Among all the formulations F9 showing the release profile (96.87%) similar to the innovator. By this evaluation results F9 was selected as the best formulation.F9 meet all the criteria specified in IP.The selected formulation was stable during the test period of accelerated stability studies.

1. INTRODUCTION

Pharmaceutical products designed for oral delivery and currently available on the prescription and over the counter markets are mostly the immediate release type, which are designed for IR of drug for rapid absorption. Disintegrating agents are substance routinely included in tablet formulation to promote moisture penetration and dispersion of matrix of dosage form in dissolution fluids[1].

The oral route of drug administration is the most popular and successfully used for conventional delivery of drugs. It offers the advantages of convenience, ease of administration, greater flexibility in the dosage form design, ease of production, and low cost. The dosage form available for administrations are solutions, suspensions, powders, tablet and capsules. The physical state of most of being solids, they are administered in solid dosage form. The solid dosage forms provide best protection to drugs against temperature, light, oxygen and stress during transportation [2]

1.1 IMMEDIATE RELEASE DOSAGE FORMS [3,4,5,6,7,8]

Immediate release dosage forms are conventional dosage forms that allow the drug to dissolve in gastrointestinal tract with no intention of delaying or prolonging the drug dissolution or absorption.Immediate drug release dosage forms disintegrate rapidly after administration with enhanced dissolution. Immediate release may be provided by way of an appropriate pharmaceutically acceptable diluents or carrier does not prolong to an appreciable extent, rate of drug release and/or absorption. These dosage form usually release (dissolve/disperse) the drug in a single action, which means the drug is released initially very quickly and then passes through the mucosal membrane in to the body, reaching the highest plasma level in a comparatively short time. Their advantage are release the drug immediately more flexibility in adjusting the dose dumping problem and can be used in initial and final stages of diseases.

1.1.1 COMPONENTS OF IMMEDIATE RELEASE DOSAGE FORMS

- Disintegrants and superdisintegrants
- Lubricants
- Diluents
- Flavors and sweeteners

1.1.2   Merits of immediate release dosage form

- ❖ Improved solubility of pharmaceutical composition
- ❖ Decreased disintegration and dissolution time for immediate release oral dosage forms
- ❖ Allows high drug loading
- ❖ Suitable for controlled/sustained release activities
- ❖ Improved stability and bioavailability
- ❖ Cost effective
- ❖ Improved compliance/added convenience
- ❖ Ability to provide advantages of liquid medication in the form of solid preparation.

1.1.3 Some Limitations of immediate release dosage forms

- ❖ In conventional oral dosage forms, there is little or no control over the release of drug and effective concentration at the target site can be achieved by intermittent administration of glossy excessive doses.
- ❖ The dosing pattern in conventional dosage results in constantly changing, unpredictable and often sub therapeutic plasma concentration, leading to marked side effects in some cases.
- ❖ The rate and extent of absorption of drug from conventional formulations may vary greatly, depending upon the factors such as physiochemical properties of the drug, excipients, various physiological factors such as the presence or absence of food, p^H of the gastrointestinal tract, and Gastro intestinal motility.
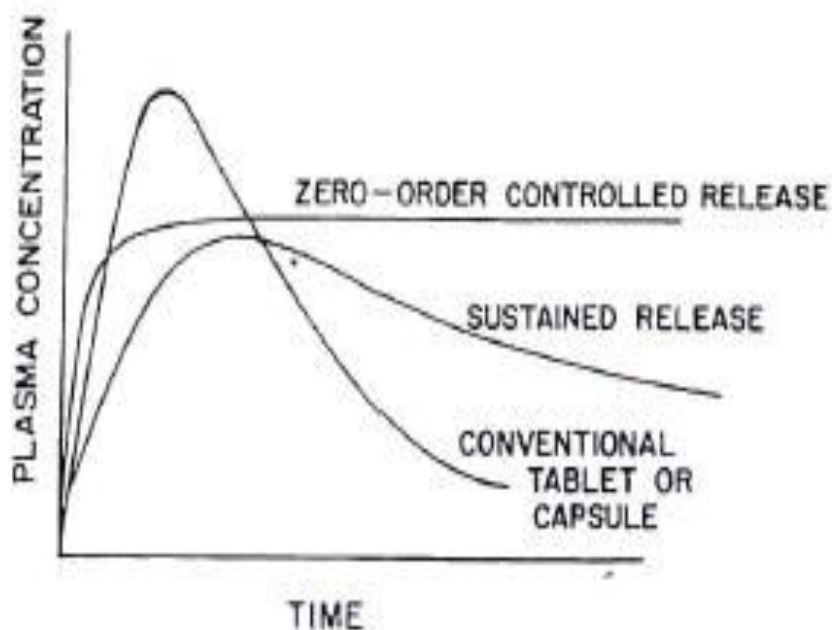
Figure1: Typical plasma drug concentration – profile for conventional tablet or

Capsule formulation, a sustained release and an oral controlled release formulation

1.2 ANTIHYPERTENSIVE DRUGS[9, 10]

Hypertension (HTN) or high blood pressure sometimes called arterial hypertension is a chronic medical condition in which the blood pressure in the arteries 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 beets (diastole).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 140/90mmHg.If this disease control on time, otherwise it may lead to heart attack, brain stroke or kidney damage

Hypertension emerged as a major public health problem worldwide. There are many factors causing hypertension, some of them occur due to heredity, gender (mostly affected in males than females), obesity, age (especially in elder persons which may due to hardening of arteries or atherosclerosis),sodium salt sensitivity, alcohol use and physical inactivity.

1.3 AMLODIPINE [11,12]

Amodipine is dihydropyridine calcium antagonist, which inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle.It is used to treat hypertension, chronic stable angina, and confirmed or suspected vaso-spatic angina.

Amlodipine is a medication used to lower blood pressure and prevent chest pain. By widening blood vessels it lowers blood pressure. In angina, amlodipine increases blood flow to the heart muscle to relieve pain due to angina. It can be used either monotherapy or combination therapy for the management of hypertension or coronary artery disease. Amlodipine can be administered to adults and children 6-17 years of age.

1.4 Classification of antihypertensives[13,14,15]

Antihypertensive are class of drugs that are used to treat hypertension (high blood pressure). Antihypertensive are classified based on their chemical structure or mechanism of action.

1. Diuretics

- ❖ Loop diuretics
    - Bumetanide
    - Furosemide
    - Ethacrynic acid
- ❖ Thiazide diuretics
    - Eptizide
    - Hydrochlorothiazide
    - Chlorothiazide

❖ Potassium sparing diuretics

- Amiloride
- Triamterene
- Spiranolactone

2. Calcium channel blockers

❖ Dihydropyridins

- Amlodipine
- Felodipine
- Nicadipine
- Nifidipine

❖ Non-dihydropyridins

- Diltiazem
- Verapamil

3. ACE inhibitors

- Captopril
- Enalapril
- Ramipril
- Benzapril
- Perindopril
- Quinapril

4. Angiotensin II receptor antagonists

- Telmisartan
- Candesartan
- Irbesartan
- Valsartan
- Olmesartan

5. Adrenergic receptors

- β blocker
    - Atenolol
    - Metaprolol
    - Nadalol
    - Nebivilol
    - Pindolol
    - Timolol
- α blocker
    - Doxazosin
    - Phentolamine
    - Prazosin
    - Terazosin
    - Tolazolin

- Mixed α+β blockers
    - Carvidilol
    - Labetalol
    - Bucindolol

6. Vasodilators

- Hydralazine
- Sodium nitroprusside

7. Adrenergic receptor agonists

- Clonidine
- Methyldopa
- Guanfacine

1.5 ANTIANGINAL DRUGS[16,17]

These drugs are used against angina. These drugs improve the myocardial perfusion and decrease the metabolic demand or possessing both the properties. The two main categories of drugs that come under these types are:-

1. ORGANIC NITRATE

2. CALCIUM ANTAGONIST ORGANIC NITRATES

1.5.1 Classification of antianginal drugs

1. Nitrates

   I. Short acting
   - Glyceryl trinitrate
   - Nitroglycerine

   II. Long acting
   - Isosorbide di nitrate
   - Isosrbide mono nitrate
   - Erythrytyl tetra nitrate
   - Penta erythritol tetra nitrate

2. β blockers

   - Metaprolol
   - Propranolol
   - Atenalol

3. Calcium channel blockers

   I.   Phenyl alkylamines
   - Verapamil

   II. Benzothiazepines
   - Diltiazem

   III. Dihydropyridines

- Nifedipine
- Amlodipine
- Felodipine

4.Pottassium channel openers

- Nicorandil
- penacidil

5. Others

- Dipyridamole
- Trimetazidine

1.5.2 The mechanism of antianginal drugs

1. Decrease myocardial oxygen consumption
2. Increase myocardial blood and oxygen supply
3. Antiplatelet ,Antithrombosis

1.5.3 Calcium channel blockers: mechanism of anti angina

1. Dilate coronary arterial
2. Reduction in peripheral vascular resistance
3. Negative chronotropic and inotropic,
   Decrease myocardic oxygen consumption
4. Protect cardiac myocytes
5. Anti atherosclerosis

1.6 TABLETS [17,18]

Tablets are solid preparations is containing a single dose of one or more active substances and usually obtained by compressing uniform volume of particles. Tablets are intended for oral administration. Some are swallowed whole, some after being chewed, some are dissolved or dispersed in water before being administered and some are retaining in

mouth where the active substances liberated. The particle consisting of one or more active substance with or without excipients such as diluents, binders, disintegrating agents , glidants,lubricants, substance capable of modifying the behavior of the preparation in the digestive tract colorings matter authorized by the competent authority and flavoring substance.

1.6.1   Advantages of tablets[19, 25, 26]

- ❖ They are unit dosage form and they offer the capabilities of all oral dosage forms for the dose precision and the least content variability during dosing.
- ❖ Accuracy and uniformity of content
- ❖ Optimal drug dissolution and hence,availability from the dosage form for absorption consistent with intended use(ie. immediate or extended)
- ❖ Usually taken orally, but can be administered sublingually,rectally or intra vaginally
- ❖ Their cost is lowest of all oral dosage forms
- ❖ They are the most compact of all oral dosage form
- ❖ Organoleptic properties are best improved by tablet coating.
- ❖ Easy to administer does not require a specialist.
- ❖ They are better suited to large scale than other unit oral forms.
- ❖ Ease of packaging (blister or strip) and easy handling over the liquid dosage forms.
- ❖ Product identification is easy and markings done with the help of grooved punches and printing with edible ink.

1.6.2 Disadvantages of tablets[27]

- ❖ Some drugs resist compression, due to their amorphous nature or low density.
- ❖ Chance of G I irritation caused by locally high concentrations of medicament.
- ❖ Difficulty in swallowing tablets in small proportion of people and so size and shape become important considerations.
- ❖ Drugs having bitter taste, objectionable odour or drugs that are sensitive to oxygen may require encapsulations or coating of tablet.
- ❖ Bioavailability problems.
- ❖ Difficulty for kids, terminally ill and geriatric patients.
- ❖ Slow onset of action compared to parenterals and solutions

1.7 Types and Classes of tablets [18,19,20,24]

Tablets are classified by their routes of administration

A. Oral tablets for ingestion

- ❖ Compressed tablets or standard compressed tablets
- ❖ Multiple compressed tablets

a) Layered tablets

b) Compression coated tablets

- ❖ Repeat action tablets
- ❖ Sustained release or modified release tablets
- ❖ Delayed action or enteric coated tablets
- ❖ Film coated tablets
- ❖ Chewable tablets

B. Tablets used in oral cavity

- ❖ Buccal tablets
- ❖ Sublingual tablets
- ❖ Trouches and lozenges
- ❖ Dental cones

C. Tablets administered by other routes

- ❖ Implantation tablets
- ❖ Vaginal tablets

D. Tablets used to prepare solutions

- ❖ Effervescent tablets
- ❖ Dispersible tablets
- ❖ Hypodermic tablets
- ❖ Tablets triturates

1.8 FORMULATION OF TABLET[22, 23, 24, 28]

Tablet generally consists of mixture of active pharmaceutical ingredients and excipients. Excipients mean any component other than active pharmaceutical ingredients. While selecting excipients for any formulation following should be considered.

- Keep the excipients to a minimum in number
- Minimize the quantity of each excipients
- Multi functional excipients may be given preference over unifunctional excipients.

1.9 ROLE OF EXCIPIENTS IN SOLID DOSAGE FORM[29]

A.DILUENTS OR FILLERS

Diluents are added the quantity of active ingredients is small or difficult to compress.Eg: sucrose, lactose, starch

B.BINDERS OR GRANULATING AGENTS

Binders help powders fuse or link particle to another.Eg: starch, povidone

C.DISINTERGRANTS

Disintegrates help the tablet breaks up after the patients ingest it.Eg: sodium starch glycolate, starch

D.LUBRICANTS

Lubricants prevent powders from sticking to the metal component of the tablet press and tablet press tooling.Eg: starch, magnesium stearate

D.GLIDANTS

Glidants are agents that are added to the tablet formulation. In order to improve the flow properties of granulation. They act by reducing inter particulate friction.

Eg: magnesium stearate, talc.

E.ADSORBENTS

Adsorbents are the substances included in the formulation that are capable of holding quantities of fluid in an apparently dry state. Oil soluble drugs, fluid extractor or oil can be mixed with adsorbents and then granulated and compressed into the tablet. Eg: magnesium carbonate, fumed silica

F.COLORANTS

Colorants are often added to tablet formulation to add value or for product identification.

G.PRESERVATIVES
These are the substances used to preserve food stuffs, wood, or other materials against decay Eg: methylparaben, propylparaben

Table no:1 Steps involved in tablet manufacturing process

S.NO	PROCESSING STEPS	DIRECT COMPRESSION	WET GRANULATION	DRY GRANULATION
1	RAW MATERIALS	YES	YES	YES
2	WEIGHING	YES	YES	YES
3	SCREENING	YES	YES	YES
4	MIXING	YES	YES	YES
5	COMPRESS	YES	NO	YES
6	WET MASS	NO	YES	NO
7	MILLING	NO	NO	YES
8	DRYING	NO	YES	NO
9	SHIFTING	NO	YES	YES
10	MIXING	NO	YES	YES
11	COMPRESSION	NO	YES	YES

1.10) STABILITY STUDIES AS PER ICH GUIDELINES[30,31]

Stability is essential factor of quality,safety ad efficacy of drug product .In theory stabilityof pharmaceutical preparation should be evaluated by exposing the product to normal shelf life conditions for year of extended periods.Generally the rate of decomposition is slow at room temperature.So such a method is time consuming and uneconomical.Therefore in practice methods are devised to accelaratethe rate of degradation by keeping the products at higher temperatures.Accelarated stability studies are used to predict the shelf life of product by accelerating the rate of decomposition ,preferably by increasing the temperature.

Stabity testing provides evidence that the quality of drug substance change with time under the influence of various enviormental conditions such as temperature , relative humidity etc.Stability studies consist of a series of test inorder to maintain an assurance of stability of drug product,namely maintenance of drug product packed in specified packaging material and stored in established storage conditions within the determined time period.

➢ AIM OF STUDY

Developing a new formula for the Amlodipine tablet IP 5mg immediate release film coated tablets, by evaluation of trial formulations and invitro dissolution profile.

➢ OBJECTIVE OF STUDY

- Carrying out literature survey of the drug molecule.
- Formulation of the tablets using different trials.
- Analyzing the trial samples.
- Optimizing the final formula.

3. PLAN OF WORK

- ➢ Development of final formula

    - Literature collection of trial product.

    - Preformulation studies.

    - Determination of Drug polymer Compatibility.

    - Formulation of trial products.

    - Dissolution studies of formulations.

    - Comparison of Dissolution profile of trials with innovator.

    - Finalization of quantitative formula.

4. LITERATURE REVIEW

- *Rajalekshmi.R* [*] *, Senthilkumar.M, Valamathi.S et al (2012)*[57]. , To develop a stable formulation of antihypertensive drug of Telmisartan and Amlodipine Besylate as an immediate release bilayer tablet. The basic aim of the study is the need to develop proper medications that control hypertension for a longer period of time. Amlodipine besylate is a long acting calcium channel blocker used in the treatment of chronic stable angina, vasospatic angina, and hypertension.Telmisartan is a potent, long acting ,non peptide antagonist of Angiotensin II(AT_1) receptor blocker , which is indicated for the treatment of hypertension.It blocks the vasoconstrictor and aldosterone – secreting effect of Angiotensin II. A total number of nine formulations have been taken to optimize and develop a robust and a stable formulation .Among the formulation tablet F_9 showed satisfactory physical parameter and found to be stable. The optimized formulation F_9 had 96.68% of drug release for telmisartan layer and 95.73% drug release for Amlodipine layer.the results suggest that the feasibility of developing bilayer tablets with two drugs Telmisartan and Amlodipine Besylate for the convenience of patients with severe hypertension.

- *N.Narasimha Rao*,*B. Radha Krishna Murthy,D.Rajasekhar et al(2013*[58]*.,* Has study the design and development of Amlodipine besylate fast dissolving tablet using natural super disintegrants.Amlodipine is sparingly soluble orally administered drug and the rate of absorption is often controlled by the rate of dissolution.The rate of dissolution can be increased by incorporating the drug in a fast disintegrating dosage form.Mucilage of natural origin is preffered over semisynthetic and synthetic substances .In this study they were developed the fast dissolving tablets of Amlodipine Besylate, using different concentrations of natural super disintegrating agents like Fenugreek seed Mucilage, Treated Agar, Modified tragacanth.From this study the concluded the Modified tragacanth shows the excellent super disintegrant prpperty and treated agar gum shows better super disintegrant property .Fenugreek seed used as disintegrant shows less disintegrant property in the formulation of fast dissolving tablets when compared to other natural polymers.

- *M.Manikandan, K.Kannan*,*S.Thirumurugu et al(2012)*[59]*.,* Has study the design and evaluation of Amlodipine besylate and Atorvastatin calcium tablets.Amlodipine Besylate is a calcium channel blocker and used for treating high blood pressure and certain types of angina and coronary heart failure.Atorvastatin calcium known as

statin used for lowering blood cholesterol and in the treatment of primary hypercholesterolemia and dyslipidemia.The main objective of this study was to formulate and evaluate an oral administerable tablet containing Amlodipine Besylate and atorvastatin calcium by wet granulation method .Among all the 4 formulations ,F4 formulation was better in all the terms of Precompression and post compression parameters. No significant change in the drug content ,physical properties and dissolution rate of the tablets after the storage of 3months at 25^0c&60%RH and 40^0c&75%RH.This study concluded that the combined pill has the potential to improve the management of hypertensive patients with additional cardiovascular risk factors.

- *Prakash Babu Dahal[*], R.Sambath kumar, K.Jaganathan, et al (2014)[60].,*has been made for the development of rapidly disintegrating tablets of Amlodipine besylate by solid dispersion technique.six solid dispersion has been prepared in different carrier formulations ratios.Dissolution study has been done for all six solid dispersion and among the best solid dispersion has been selected and used for the tablet formulation.In this study ,fast disintegrating tablet were prepared by using the different super disintegrants like crospovidone,cross caramallose sodium,Agar and guar gum . The effect of various superdisintegrants on disintegration behaviour of tablets was evaluated in phosphate buffer P^H 0.01 N HCL.All the formulations were evaluated for the pre compression and post compression parameters. Wetting time of the formulations containing Crosspvidone and Agar was least and tablet showed fastest disintegration.FT-IR studies revealed that thre is no physio chemical interaction between Amlodipine Besylate and other exicipients.Amongst all the formulations F_6 prepared by both the combination of crospovidone and Agar showed least disintegrating time and faster dissolution of 98.04%.

- *Avinash Mahatme[1],Vijay R. Mahajan[1],V.R Gudsoorkar[2],et al(2015)[61].,*has study the formulation and evalution of immediate release tablet of Amlodipine Besylate.The FT-IR study was also conducted and there is no iteraction between the drug and the exicipients.The immediate release tablet was prepared by using the exicipients like SSG,Cross povidone,Cross caramallose by wet granulation method.Thus the prepared A4 batch of Amlodipine containing higher concentration of SSG ie. 10% released 95.98% drug within 1hrs. Stability data of optimized batch of tablets revealed that

there were no changes observed in the appearance , drug content, dissolution profile which showed that immediate release tablet is stable at 40 ± 2^0c/$75\pm5\%$RH.

- *Behin sundara raj et al(2012)*[62] *.,*has study the formulation and characterization of fast disintegrating tablets of Amlodipine using super disintegrants by direct compression method.crospovidone and sodium starchglycolate as thesuperdisintegrants.combination of both superdisintegrant shows least disintegration time and faster dissolution of 87%.combination of super disintegrant is better suited for the development of fast disintegration tablet.

- *Methaq.H.Sabar et al (2013)*[63] *.,*Has study the preparation and invitro evaluation of fast dissolving film of amlodipine besylate solid dispersion ,and the release increased with increasing the ratio of PEG 6000 or PVP in solid dispersion increased the release rate and the solvent evaporation method gave greater release than the fusion method.In fast dissolving film it was seen that the concentration of SCMC increased the release rate and decrease significantly and as the concentration of glycerin increased the release rate increased significantly.

- *Jaimin Modi et al (2016)*[64] *.,*has study the formulation evaluation &optimization of immediate release tablet of fexofenadine hydrochloride .the invitro dissolution studies show the release in following order of super disintegrants.cross caramallose>sodium starch glycolate.Drug release mechanism in all media(P^H1.2,P^H4.0,P^H6.8)was found as diffusion controlled.(ie.,n value-0.219 to 0.042).Higuichi square root law indicates the drug release follows diffusion release mechanism.

- *Anjum et al (2014)*[65] *.,*has study the assessment of pharmaceutical quality control and equivalence of various brands of amlodipine besylate (5mg)tablets available in the Pakistani market under biowaiver conditions.dissolution test done in various medias (Distilled water,P^H 1.2, P^H 4.5,P^H6.8).Under biowaiver conditions all the generics are interchangable with innovator;they are therapeutically equivalent.

- *Oyeniyi et al(2016)*[66] *.,*has study the comparative pharmaceutical evaluation of amlodipine (5mg)tablets registered in Nigeria by NAFDAC,and marketed by various pharmaceutical companies nationwide.All the brands evaluated achieved 85% release of the active ingredient within 30 min,in all the dissolution media with P^H1.2,4.5,6.8 and the release of all the brands are similar at various P^H values used.

- *S.Suresh et al(2011)[67].,*has study the formulation and evaluation mouth dissolving tablet of Amlodipine besylate by using the threesuper disintegrants viz.,hypromellose,crospovidone and sodium starch glycolate at different concentration with microcrystalline cellulose.Among three super disintegrants crospovidone F7 emerged as overall best formulation.

- *Soham shukla et al(2013)[68].,*has study the formulation,optimization and evaluation of immediate release bilayer tablet of Temisartan and amlodipine besilate using full factorial design.TF6was optimized in telmisartan layer which contained meglumine 7.5%(16mg)and crospovidone 5%(11mg)and AF7was optimized in amlodipine layer which contained starch paste 5%(5mg)and croscaramallose sodium 3%(3mg).

- *Shoba krushnan et al (2016)[69].,*has study the formulation and evaluation of orodispersible tablet of amlodipine besilate.Formulation containing higher concentration of sodium starch glycolate and crospovidone as superdisintegrant showed better dissolution profile and disintegration time.FT-IR and DSC were conducted for drug exicipients compatibility study.

- *Mayur et al (2013)[70].,*has study the immediate release tablet of antihypertensive drug olmesartan medoxomile. Effect of different fillers and disintegrants were also explored . microcrystalline cellulose ,lactose monohydrate,were used in wet granulation.final selection of the formula based on the pharmaceutical equivalence of developement formulation to that of marketed one.

- *Narmada G Y et al(2009)[71].,*Has study the formulation evalution and optimization of fast dissolving tablets containing amlodipine besylate by sublimation method.Sublimation method was adopted to prepare the tablets using 2^3 fullfactorial design.FT-IR and DTA conducted for the compatibility of drug with exicipients.The results obtained showed that the quantity of starch potato, sodium starch glycolate,camphor significantly affect the response variables.

- *Nyol et al(2013)[72].,*has done a review related to the immediate release dosage forms for fulfill the medical needs ,formulators have devoted considerable effort to developing novel type of tablet dosage form for oral administration ,one that disintegrates and dissolve rapidly with enhanced dissolution.An extension of market exclusivity ,which can be provided by immediate release dosage form,leads to increased revenue,while also targeting undeserved and under-treated patient populations.

5. DRUG AND EXICIPIENTS PROFILE
5.1 DRUG PROFILE

5.1.1AMLODIPINE DRUG PROFILE[32,33,34,37]

Figure No: 2 structural formula
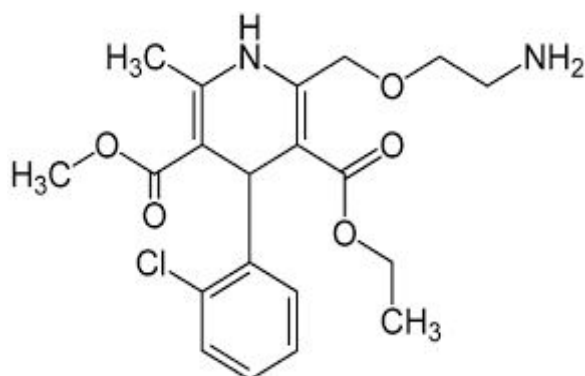
Table No: 2

Properties	Information
Molecular Formula	$C_{20}H_{25}ClN_2O_5$
Molecular weight	408.879 g/mol
IUPAC	3 Ethyl 5 Methyl 2-[(2-Aminoethoxy]-4-(2-chlorophenyl)-6-Methyl-1,4-Dihydropyridine-3,5Dicarboxylate
Macroscopic Appearance	White crystalline powder
Half life	30-50 hours
Solubility	Water-slightly soluble Methanol-freely soluble Ethanol-sparingly soluble 2- propanol-sligtly soluble
p^H	1-6 at 37^0C
p^{Ka}	8.6
Use	Anti hypertensive,anti anginal

5.1.2 MECHANISAM OF ACTION OF AMLODIPINE[35, 36]

Pharmacokinetically it is the most distinct Dihydropyridines (DHP).They lower Bp by decreasing peripheral resistance without compromising cardiac output .Despite vasodialation, fluid retention is insignificant. Also inhibit transmembrane influx of calcium ions into vascular smooth muscles and cardiac muscles.It is indicated for the treatment of hypertension, chronic stable angina, and confirned or suspected vasospatic angina.

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

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

5.2 EXCIPIENTS PROFILE

5.2.1 STARCH[38]

Table No:3 starch excipient profile

Non proprietary Names	Amylum,Polysaccharide
Synonyms	Starch1500,Starch LM
Empirical formula	$(C_6H_{10}O_5)_n$
Molecular weight	Depends on extent of gelatinization
Description	White color, tasteless
Functional categories	Thickening agent, stiffening agent, gluing agent
Solubility	Insoluble in cold water or alcohol, Becomes soluble in water on heating
Stability and storage condition	Starch is stable and should be stored in a well closed container in a cool ,dry place
Incompatibilities	Incompatible with strong acids,alkali.Avoid mixing with strong oxidizing agents
Applications	Binder, Disitegrant, Flow aid, Lubricant

5.2.2 SODIUM STARCH GLYCOLATE[39]

Table No: 4 sodium starch glycolate excipient profile

Non proprietary Names	Explotab,Vivastar
Synonyms	Sodium salt ofcarboxymethyl ether of starch
Empirical formula	C_2H_5ONa
Molecular weight	500000-11000000
Description	White to off- white, Tasteless, odorless, relatively free flowing powder
Functional categories	Disintegrant, Dissolution aid, Suspending agent
Solubility	Practically insoluble in organic solvents. Absorbs water rapidly
Melting point	338^0C
Stability and storage conditions	Store in well closed container to protect from humidity
Incompatibilities	Mostly compatible with all other tableting ingredients
Applications	Suspending and gelling agent

5.2.3 LACTOSE[40]

Table No: 5 Lactose excipient profile

Non- proprietary Names	Lactose monohydrate ph Eur: Lacto sum(BP) Lactose monohydrase(USP)
Synonym	Fast-flo,Lactohem, Microtose, Pharmatose
Empirical formula	$C_{12}H_{22}O_{11}.H_2O$
Molecular weight	360.31
Description	White off white to crystalline particles or powder. Odorless and slightly sweet tasting
Functional categories	Tablet and capsule diluents
Solubility	Freely soluble in water
Melting point	201-202^{0C}
Stability and storage conditions	Under humid conditions (80% relative humidity and above), mold growth may occur. Lactose may develop a brown coloration on storage. Lactose should be stored in a well closed container in a cool, dry place.
Incompatibilities	Lactose incompatible with aminoacids,aminophylline,amphetamine
Applications	Filler or diluents, Binder

5.2.4 TALC[41]

TableNo: 6 Talc excipient profile

Non proprietary names	B.P – purified talc JP-Talc Ph Eur-Talcum USP-Talc
Synonyms	At talc, Hydrous magnesium calcium silicate, Hydrous magnesium silicate,Magsil osmanthus,Purified French chalk Magnesium hydrogen meta silicate,soapstone
Empirical formula	$Mg_3Si_4O_{10}(OH)_2$
Molecular weight	379.27
Description	Talc is very fine, white to grayish white, odorless, unctuous, crystalline powder. It adhere rapidly to the skin and is soft to the touch and free from grittiness
Melting point	150^0C
Solubility	Not soluble in water and slightly soluble in dilute mineral acids, insoluble in water and ethanol
Functional categories	Anti caking agent,glident,diluents and lubricant for tablets and capsules
Stability and storage conditions	Talc is stable material and may be sterilized by heating at 160^0c for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or uv radiations. Talc should be stored in a well closed container in a cool, dry place.
Incompatibilities	Incompatible with quaternary ammonium compounds
Applications	Lubricant, Diluent,dissolution retardant in controlled release formulations

5.2.5 MAGNESIUM STEARATE[39]

Table No: 7 Magnesium stearate excipient profile

Non proprietary names	BP-Magnesium stearate JP-Magnesium stearate PhEur-Magnesium stearate
Synonyms	Dibasic magnesium stearate;Magnesium distearate;Magnesium octadeconoate;octadecanoic acid; Magnesium salt
Empirical formula	$C_{36}H_{70}MgO_4$
Molecular weight	591.24
Description	Magnesium stearate is very fine, light white, precipitated or milled, impalpable powder with low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.
Functional categories	Tablet and capsule lubricant
Solubility	Practically insoluble in ethanol (95%), ether and water, slightlysoluble in warm benzene and warm ethanol (95%).
Melting point	117-150^{0}C
Stability and storage conditions	Magnesium stearate stable and should stored in a well closed container in a cool, dry place
Incompatibilities	Incompatible with strong acids,alkalies,andiron salts.Avoid mixing with strong oxidizing materials
Applications	It is primarily used as lubricants in tablet and capsule manufacture

5.2.6 METHYL PARABEN[42]

TableNo:8 Methyl paraben excipient profile

Non proprietary names	Sodium methyl para hydroxyl benzoate, methyl paraben sodium salt
Synonyms	Methyl 4-OH benzoate,NipaginM
Empirical formula	$C_8H_8O_3$
Molecular weight	152.14732
Description	Colorless crystals or white crystalline powder
Solubility	Soluble in water at 25^0C, slightly soluble in benzene,CCl_4,ehanol,ether, acetone,DMSO,methanol
Stability and storage conditions	Stable at ambient temperature and under normal condition of use dust may be explosive. Store in a cool dry and well ventilated place,keep container closed when not in use.
Melting point	125-128^{0}C
Functional category	Preservative
Incompatibilities	Incompatible with alkalies and metal salt
Application in pharmaceutical industry	It is an antifungal agent, often used in variety of cosmetics and personal care products. It is also used as food preservative. Fungicide in Drosophila food media

5.2.7 PROPYL PARABEN[43, 44]

Table No: 9 propyl paraben excipient profile

Non proprietary names	Propylis parahydroxybenzoate (Latin) Propyl 4- hydroxybenzoat (German) Propyle(parahydroxybenzoate de) (French)
Synonyms	Propyl butex,Propyl chemosept, Propyl 4-OH benzoate, Propyl Para-OH benzoate, Para OH benzoic acid propyl ester
Empirical formula	$C_{10}H_{12}O_3$
Molecular weight	180.2
Description	White crystalline powder ,colorless crystsls or white powder or chunky white solid,odorless or faint aromatic odour,low toxicity and tasteless
Solubility	Water soluble
Melting point	95-98^{0}C
Stability and storage conditions	Stable, stability maximum occurs at p^H 4-5
Functional category	Preservative ,food additive
Incompatibility	Incompatible with alkalies and metal salts
Application in pharmaceutical industry	An antimicrobial, Preservative in packaged foods, pharmaceuticals, cosmetics, personal care products

6. METHODOLOGY

6.1 PRE- FORMULATION STUDIES [45,46,47, 48,49]

Preformulation studies is an investigation of physical and chemical properties of a drug substance alone or in combination with excipients. It is the first step in the rational development of the dosage forms.

A) Physiochemical evaluation of a drug molecule

1) Description

2) Solubility

3) P^H

4) Melting point

5) Chemical nature

6) Hygroscopicity

7) Loss on drying

8) Particle size determination

9) Flow properties

B. Compatibility studies of the drug molecule with excipients

The information obtained from preformulation studies indicates many of the subsequent events and approaches to be taken into consideration during formulation development. It is imperative to ensure the ingredients used are compatible with one another. Incompatibility occurs between the drug and excipients and the excipients themselves. Incompatibilities manifested through many modes, such as acid base interaction and complex formation, result in lower potency or stability and eventually, poor therapeutic efficacy of the product .Therefore it is essential to avoid incompatibilities, and this is achieved by carrying out studies to detect potential interactions between the components used in the formulation.

A.PHYSIOCHEMICAL PARAMETERS

1)Description

Atypical preformulation study should begin with the description of the drug substance.ie the color, odour and taste of the new drug must be recorded.It kept as reference for comparing with the other batches during the production.

2) Solubility

Preformulation studies focuses on drug solvent system that could occur during delivery of the drug molecule. So understanding the solubility profile of drug regarded as the one of the most important aspect of preformulation testing, especially for those drugs which are administered as oral dosage forms,parenterals and also the drugs which are unstable on contact with solvent.Solubility is related to the strength of solute-solvent bond strength and interaction between the solute and the solvent.

3) p^H

The p^H is the measure of negative logarithm of hydrogen ion concentration of an aqueous solution. It is one of the most important factors from which the stand point of solubility, stability and physiochemical suitability of a formulation. The p^H value of a solution is determined potentiometrically by means of a glass electrode.

4) Melting point

A temperature at which the first particle of the substance completely melts is regarded as melting point of the substance, and also at which the first particle starts to melt and last particle completely melts is regarded as the melting range

5) Chemical nature

Solubility, stability, bio availability etc., a substance is depends on its chemical nature and this information helps to design a suitable dosage form

6) Hygroscopicity

It is defined as ability of a substance to absorb moisture from the environment it exposed

Table No: 10 Moisture absorption analysis

S.NO	NATURE OF SAMPLE	RESULT OF THE DETERMINATION
1	Deliquescent	Sufficient water absorbed to form a liquid
2	Very hygroscopic	Increase in mass equal to or more than 15%
3	Hygroscopic	Increase in mass less than 15% and equal to or more than 2%
4	Slightly hygroscopic	Increase in mass less than 2% and equal to or more than 0.2%

7) Particle size determination

Particle size determination is an important factor which determines number of parameters like dissolution rate, bioavailability, content uniformity, flow properties, texture and stability of a formulation. The particle size can be analyzed by number of methods like sieving, optical microscopicy, and laser diffraction methods .The particle size of Amlodipine analyzed by sieving method

Sieve analysis

Table No: 11 Classification of sample based on the % of sample retained or passed on test sieve.

S.NO	NATURE OF SAMPLE	RESULT OF DETERMINATION
1	Coarse powder	NLT 95%of the sample mass pass through 14# And NMT40% pass through 36#
2	Moderately coarse powder	NLT 95%of the sample mass pass through 25# and NMT40% pass through 60#
3	Moderately fine powder	NLT 95% of the sample mass pass through 36# and NMT40% pass through 100#
4	Fine powder	NLT 95% of the sample mass pass through 100 # and NMT 40% pass through 150#
5	Very fine powder	NLT 95% of the sample mass pass through 150# and NMT 40% pass through 200#
6	Super fine powder	NLT 90% by number of particle are less than 10µm

9) Flow property measurement

It is a very important parameter affects the mass uniformity of the dose .Usually flow properties are predicted interms of angle of repose, bulk density, and tapped density.

ANGLE OF REPOSE

The angle of repose has been used to characterize the flow properties of solids. It is related to inter particulate friction or resistance to movement between particles.It is the maximum angle possible between surface of the pile of powder or granules and the horizontal plane.

$$\theta = Tan^{-1} \, h/r$$

Where

       θ =angle of repose

       h =height of the pile

       r =radius

Method: a funnel was fixed at a height approximately of 2-4 cm over the platform. The loose powder was slowly passed along the wall of funnel, till the cone of powder formed. Determine the angle of repose by measuring the height of the cone of powder and radius of the heap of the powder.

Table No: 12 flow properties and corresponding angle of repose

S.No	FLOW PROPERTY	ANGLE OF REPOSE
1	Excellent	$25\text{-}30^0$
2	Good	$31\text{-}35^0$
3	Fair	$36\text{-}40^0$
4	passable	$41\text{-}45^0$
5	Poor	$46\text{-}55^0$
6	Very poor	$56\text{-}65^0$
7	Very very poor	$>66^0$

Bulk density (BD) and tapped density (TD)

Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. It is of great importance in case of the tablet and capsule manufacturing process, especially in size of a high dose capsule product or the homogeneity of low dose formulations in which there is a large difference in drug and the excipients densities. In addition to the bulk densities, there is desirable to know the true density of the powder for computation of void volume or porosity of packed powder beds

An accurately weighed quantity of powder poured to a graduated measuring cylinder and volume measured. Graduated cylinder closed with a lid and and set in to the tap density tester. After the volume measured and continued the operation till the two consecutive reading where equal. The bulk density and tapped density were calculated by the following formulae

> **Bulk density=weight of the sample in gram ÷volume occupied by the sample**

> **Tapped density=Weight of the sample in gram ÷Tapped volume**

Compressibility index (CI) and Hausner's (HR) ratio

The compressibility index and Hausner's ratio are used for predicting powder flow property .Both the compressibility index and Hausner's ratio were determined by using the bulk density and tapped density of the powder

Compressibility index= tapped-untapped*100 ÷ tapped

H.R= tapped density ÷ bulk density

Table No: 13 Relation of flow property with Hausner's ratio & compressibility index

Compressibility index	Flow property	Hausner's ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very very poor	>1.60

6.2 MATERIALS AND EQUIPEMENTS

Table No: 14 List of materials for preparation of Amlodipine tablets

S.NO	Name of Materials used	Specification	Use
1	Amlodipine	IP	Active ingredient
2	Starch	IP	Disintegrant
3	Sodium starch glycolate	IP	Super disintegrant
4	Magnesium stearate	IP	Lubricant
5	Talc	IP	Filler or diluent
6	Lactose	IP	Glidant
7	Methyl paraben	IP	Preservative
8	Propyl paraben	IP	Preservative

Table No: 15 List of equipment used in formulation and evaluation of Amlodipine Tablets

S.NO	INSTRUMENTS USED	MANUFACTURER
1.	Electronic weighing balance	Mettler,Switzerland
2.	Electronic weighing balance 1kg	Avery India
3.	Max mixer	Innofab india pvt limited Hyderabad
4.	Fluidized bed dryer	Alliance Bombay
5.	Cad mill	Cadmach Ahmadabad
6.	Blender	Bhuvaneswari,Chennai
7.	Tablet compression machine 45 station double rotary	Cadmach Ahmadabad
8.	Friability tester	Veego Mumbai
9.	Tablet hardness tester	Electrolab ,Mumbay
10.	Bulk density apparatus	Elecrolab Mumbay
11.	Dissolution apparatus USPII	Veego,Mumbay
12.	Tablet disintegration apparatus	Veego ,Mumbay
13.	FT-IR spectrophotometer	Perkin elmer,USA
14.	HPLC	Shimadzu,Mumbai
15.	Tray dryer	Gansons,Chennai

6.3 PROCESS INVOLVED IN TABLET PRODUCTION

Figure No: 3 Flow chart of process involved in tablet production

DRUG   EXCIPIENTS

SIEVING AND WEIGHING

DRY MIXING

BINDER PREPARATION

WET GRANULATION

DRYING

PULVARISATION

LUBRICATION

COMPRESSION
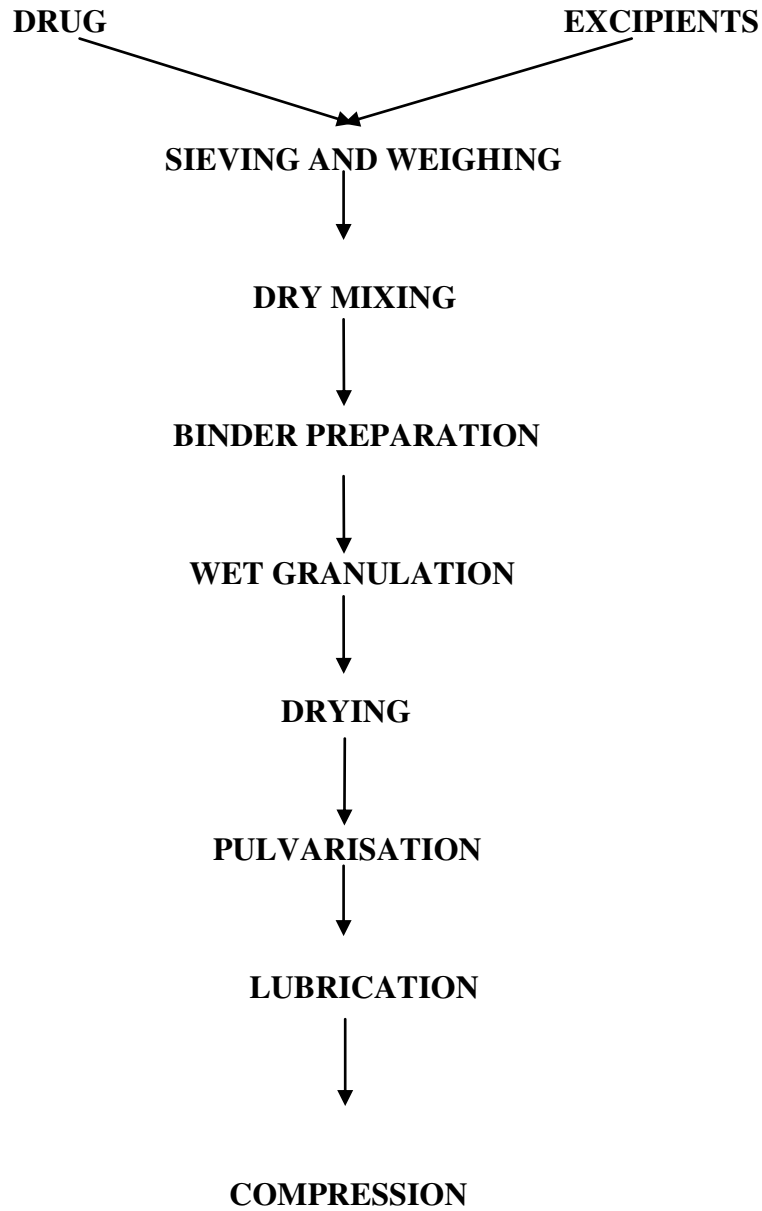
Steps involved in amlodipine granules

Amldipine granules for tablets production are prepared by the following steps

Dry mixing: Check the weight of amlodipine and sift through the 12 #and load in a Max mixer and dry mix for 10 minutes at a low speed

Granulation: Add binder solution in the above powder which mixing for 5-10 min at slow speed. Change mill speed to fast and mix for 5-15 minutes till required end point achieved. Add excess amount of water if it is required. After mixing of powder scrap material from the Max mixer and mill the wet mass through Cad mill load in the bowl of the Fluidized bed dryer.

Drying: dry the wet milled granules in tray dryer for 6 hours at 60^0C . Dry till the loss on drying achieved.

Pulverization: Dried granules from the tray dryer is passed through the Cad mill for the size reduction.After getting the uniform sized particles passes through respective mesh for the size uniformity. Collect the granules in a container and load in a double cone blender.

Blending: Load the granules in octagonal blender and blend for 5 minutes at an rpm speed. And sift the sodium starch glycolate and magnesium stearate , talc, lactose through the 40# to the blender and blend for 5 minutes

6.4 Formulation development comparative data of Amlodipine Ip 5mg immediate release film coated tablets(n=9)

Table no.16 Formulation development comparative data of Amlodipine IP 5mg film coated tablets.

S.No	Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
1	Amlodipine (mg)	7	7	7	7	7	7	7	7	7
2	Starch (mg)	45	50	55	45	50	55	45	50	55
3	Sodium starch glycolate(mg)	-	-	-	1	2	3	1	2	3
4	Lactose (mg)	39.4	34.4	29.4	41.4	35.4	29.4	38.4	32.4	26.4
5	Talc (mg)	5	5	5	5	5	5	5	5	5
6	Magnesium stearate(mg)	3	3	3	-	-	-	3	3	3
7	Methyl paraben(mg)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
8	Propyl Paraben(mg)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
9	Coating material sunset yellow(mg)	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005
	Total % amount	100	100	100	100	100	100	100	100	100

6.4 Formulation development comparative data of various formulations Amlodipine IP 5mg film coated tablets.

F$_1$

Table no: 17 Formula for Amlodipine(F$_1$)IP 5mg film coated tablets.

S.NO	INGREDIENTS	QUANTITY
1	Amlodipine	7mg
2	Starch	45mg
3	Sodium starch glycolate	-
4	Lactose	39.4mg
5	Talc	5mg
6	Magnesium stearate	3mg
7	Methyl paraben	0.5mg
8	Propyl paraben	0.1mg
9	Coating material sunset yellow	.005mg
	Total % amount	100mg

F₂

Table no: 18 Formula for Amlodipine(F_2)IP 5mg film coated tablets.

S.NO	INGREDIENTS	QUANTITY
1	Amlodipine	7mg
2	Starch	50mg
3	Sodium starch glycolate	_
4	Lactose	34.4mg
5	Talc	5mg
6	Magnesium stearate	3mg
7	Methyl paraben	0.5mg
8	Propyl paraben	0.1mg
9	Coating material sunset yellow	0.005mg
	Total % amount	100mg

F₃

Table no: 19 Formula for Amlodipine(F₃) IP 5mg film coated tablets.

S.NO	INGREDIENTS	QUANTITY
1	Amlodipine	7mg
2	Starch	55mg
3	Sodium starch glycolate	-
4	Lactose	29.4mg
5	Talc	5mg
6	Magnesium stearate	3mg
7	Methyl paraben	0.5mg
8	Propyl paraben	0.1mg
9	Coating material sunset yellow	0.005
	Total % amount	100mg

F₄

Table no: 20 Formula for Amlodipine (F₄) IP 5 mg film coated tablets.

S.NO	INGREDIENTS	QUANTITY
1	Amlodipine	7mg
2	Starch	45mg
3	Sodium starch glycolate	1mg
4	Lactose	41.4mg
5	Talc	5mg
6	Magnesium stearate	-
7	Methyl paraben	0.5mg
8	Propyl paraben	0.1mg
9	Coating material sunset yellow	0.005mg
	Total % amount	100mg

F₅

Table no: 21 Formula for Amlodipine(F₅) IP 5mg film coated tablets.

S.NO	INGREDIENTS	QUANTITY
1	Amlodipine	7mg
2	Starch	50mg
3	Sodium starch glycolate	2mg
4	Lactose	35.4mg
5	Talc	5mg
6	Magnesium stearate	-
7	Methyl paraben	0.5mg
8	Propyl paraben	0.1mg
9	Coating material sunset yellow	0.005mg
	Total % amount	100mg

F₆

Table no: 22 Formula for Amlodipine (F_6) IP 5mg film coated tablets.

S.NO	INGREDIENTS	QUANTITY
1	Amlodipine	7mg
2	Starch	55mg
3	Sodium starch glycolate	3mg
4	Lactose	29.4mg
5	Talc	5mg
6	Magnesium stearate	-
7	Methyl paraben	0.5mg
8	Propyl paraben	0.1mg
9	Coating material sunset yellow	0.005mg
	Total % amount	100mg

F₇

Table no: 23 Formula for Amlodipine(F₇) IP 5 mg film coated tablets.

S.NO	INGREDIENTS	QUANTITY
1	Amlodipine	7mg
2	Starch	45mg
3	Sodium starch glycolate	1mg
4	Lactose	38.4mg
5	Talc	5mg
6	Magnesium stearate	3mg
7	Methyl paraben	0.5mg
8	Propyl paraben	0.1mg
9	Coating material sunset yellow	0.005mg
	Total % amount	100mg

F₈

Table no: 24 Formula for Amlodipine(F₈) IP 5mg film coated tablets.

S.NO	INGREDIENTS	QUANTITY
1	Amlodipine	7mg
2	Starch	50mg
3	Sodium starch glycolate	2mg
4	Lactose	32.4mg
5	Talc	5mg
6	Magnesium stearate	3mg
7	Methyl paraben	0.5mg
8	Propyl paraben	0.1mg
9	Coating material sunset yellow	0.005mg
	Total % amount	100mg

F₉

    Table no: 25 Formula for Amlodipine (F₉) IP 5 mg film coated tablets.

S.NO	INGREDIENTS	QUANTITY
1	Amlodipine	7mg
2	Starch	55mg
3	Sodium starch glycolate	3mg
4	Lactose	26.4mg
5	Talc	5mg
6	Magnesium stearate	3mg
7	Methyl paraben	0.5mg
8	Propyl paraben	0.1mg
9	Coating material sunset yellow	0.005mg
	Total % amount	100mg

6.6 COMPRESION OF TABLETS

6.6.1 Compression parameters:-

The compression is done by using CADMACH 45 station compression machine specially designed for the compression of tablets having two different hoppers for the flow of granules. Two punches are setting in the compression machine for the compression of the tablets. The pressure adjustment devices are used to adjust the pressure in the machine. It helps to adjust the weight of the tablet. The granules are passed through the two hoppers, and are filled in the die cavity and the final compression takes place with desired weight and the hardness being set. Due to the pressure on the upper and the lower punch the granules are compressed to get the tablet.

Weight and the content uniformity of tablet are tested.

Punch specification:-

Upper punch: 6mm plain round with biweled edges and kg embossed upper punch

Lower punch: 6mm plain round with biweled edges lower punch

Temperature and relative humidity record

Temperature: $25\text{-}26^0$C

Relative Humidity: 45-55%

6.6.2 Compression parameter

Description of tablet :Orange colored round tablet

Weight of 20tablets : 2.2767g

Hardness   : 4.4kg/cm^2

Friability   : 0.0525%

Thickness   : 3.4mm

Disintegration time : 15 minutes

Individual tablet weight variation: 108mg-119mg
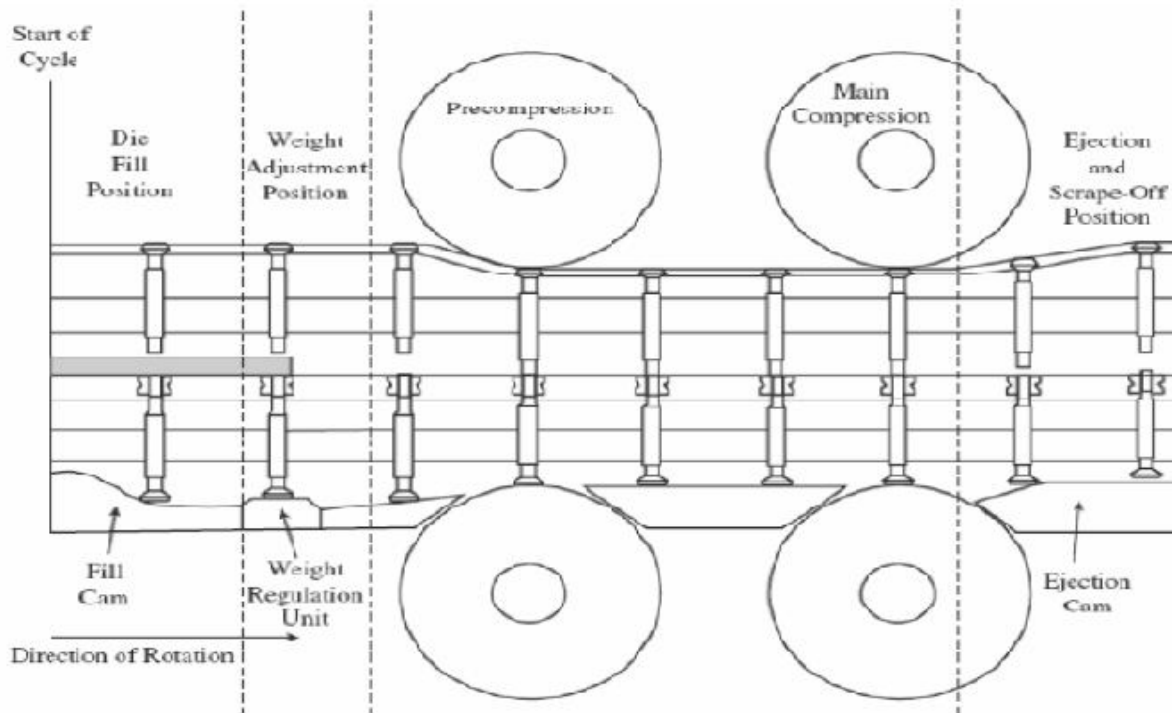
Figure No. 4 Compression process

6.7 COATING PROCEDURE

Coating is done by using the Glatt tablet hi coater with an optimized parameter for uniform coating of the tablets without any rough service on the tablet and uniformity in the coating achieved by stirring the coating solution continuously during coating and the percentage of coating is properly checked by taking the average initial weight of 50 tablets before coating and after coating.

6.7.1 Coating parameters:-

Inlet temperature: 52-55^{0}C

Exhaust temperature: 38-42^{0}C

Atomization pressure: 3 kg/cm^2

Pan rpm: 4 rpm

Gun bed distance: 20-30 cm

Spray rate: 60 ml/min/3guns

Peristal pump rpm: 8-12 rpm

6.8 POST COMPRESSION PARAMETERS [50,51]

The quantitative evaluation and assessment of a tablets,chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. These properties are important since chemical breakdown or interaction between tablet components may alter the physical tablet properties, and greatly affect the bioavailability of the tablet system. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. This includes the diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characters. The diameter and the shape depend on the die and punches selected for the compression of tablets. The remaining specifications assure that tablets do not vary from one production lot to another. The following standards or quality control tests should be carried out on compressed tablets.

1. General appearance

The general appearance of tablets, visual identity and overall 'elegance' is essential for consumer acceptance, control of lot-to-lot uniformity and general tablet uniformity and for monitoring the production process. The control of general appearance involves measurement of attributes such as a tablet's size, shape, color, presence or absence of odour, taste, surface textures, physical flaws and consistency.

2. Size and Shape

The type of tooling determines the shape and the dimensions of compressed tablets during the compression process. At a constant compressive load, tablets thickness varies with the changes in die fill, particles size distribution and packing of the powder mix being compressed and with tablet weight, while with a constant die fill, thickness

varies with variation in compressive load. Tablet thickness is consistent from batch to batch or within a batch only if the tablet granulation or powder blend is adequately consistent in particle size and particle size distribution, if the punch tooling is of consistent length, and if the tablet press is clean and good working condition.

3. Thickness

The thickness of individual tablet may be measured with a micrometer, which permits accurate measurements and provides information of the variation between the tablets. Tablet thickness should be control within a ±5% variation of a standard value. Any variations within a particular lot of tablets or between manufactures lots should not be apparent to the unaided eye for consumer acceptance of the products. In addition thickness must be controlled to facilitate packaging. The physical diamension of tablet along with the density of the material in the tablet formulation and their proportions, determine the weight of the tablet. The size and the shape of the tablet can also influence the choice of the tablet machine to use, the best particle size for granulation, production lot size that can be made, the best type of tablet processing that can be use, packaging operations and the cost of production.

Six tablets from were randomly selected from each batch and their thickness was measured by using Vernier callipers. The average thickness with standard deviation of the tablets from each batch were measured.

4. Weight variation[52,53]

This test is also known as uniformity of weight. This does not apply to layer or enteric coated tablet. Weight of individual 20 tablets was noted and their mean weight was calculated, and the percentage deviation was calculated by using the formula.

$$\text{Percentage deviation} = \frac{X - X^1}{X} \times 100$$

Where,

X = actual weight of the tablet

X^1 = average weight of the tablet

Table No. 26 weight variation specification

IP/BP	LIMIT	USP
80mg or less	10%	130mg or less
More than 80mg or less than 250mg	7.5%	130mg to 324mg
250mg or more	5%	More than 324mg

5. Content uniformity

The content uniformity test is used to ensure that every tablet contain the amount of drug substance intended with little variation among tablet within a batch due to increased awareness of physiological availability. The content uniformity test has been included in the monograph of all coated and uncoated tablets and all capsules intended for oral administration where the ranges of size of the dosage form available include 50mg or smaller sizes. Tablet monograph with a content uniformity requirements do not have weight variation requirements.

6. Friability

Friction and shock are the forces most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and is designed to evaluate the abilility of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by use of Roche fribilator. A number of tablets are weigh and placed in the apparatus . They are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After 4 minute of this treatment of 100 revolutions the tablets are weighing and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The values expressed as percentage. A maximum weight loss of not more than 1% of the tablet being tested during the friability test is consider generally acceptable and any broken or smashed tablet are not picked up. Normally, when capping

occurs friability values are not calculated. A thick tablet may have fewer tendencies to cap whereas thin tablets of large diameter often show expensive capping, thus indicate in that tablets with greater thickness have reduced internal stress.

$$\text{Friability index} = \frac{\text{initial weight} - \text{final weight}}{\text{Initial weight}}$$

7. Hardness

The resistance of tablet to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness it is now designated as either the Monsanto or Pfizer hardness tester .The instrument measure the force required to break the tablets when the force generated by a coil spring is applied diametrically to the tablet.

Hardness which is now more appropriately called crushing strength determinations are made during tablet production and are used to determine the need for pressure adjustment on tablet machine. If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specification; if it is too soft, it may not be able to withstand the handling during subsequent processing. Such as coating or packaging and shipping operation. The force required to break the tablet is measured in kilograms and crushing strength of $4 kg/cm^2$ usually consider to the minimum for satisfactory tablets. Oral tablet normally have the hardness 4- $10 kg/cm^2$;However,hypodermic and chewable tablet are usually much softer($3 kg/cm^2$) and some sustained release tablet are much harder(10-$20 kg/cm^2$).Tablet hardness associated with other tablet properties such as densities and porosity. Hardness generally increases with normal storage of tablet and depends on the shape, chemical properties, binding agents and pressure applied during compression.

8. Dissolution.

Dissolution is the process by which a solid solute enters a solution. In the pharmaceutical industry it may be defined as the amount of drug substance that goes in to solution per unit time under standardized conditions of liquid/solid interphase, temperature and solvent composition.

Dissolution behavior of drug has a significant effect on pharmacological activity in fact a direct relationship between in vitro dissolution rate of many drugs and their solid dosage forms may or may not disintegrate when they interact with gastro intestinal fluid following oral administration depending on their design.Dissolution kinetics is important in determining the bioavailability of a drug .A variety of designs of apparatus for dissolution testing have been proposed and tested, varying of simple beaker with stirrer to complex systems. The choice of apparatus to be used depends largely on the physiochemical properties of the dosage forms.

The two types of methods are employed for performing the in vitro dissolution studies

1. Basket type

2. Paddle type

Basket type

Basket method is used for evaluating the formulations that tend to float by carrying out the dissolution study. flotting is due to swelling of the formulation by taking some amount of dissolution medium. So in this method the formulation is entrapped inside the basket that will not allow the formulation to float even if it swells and becomes lighter than the dissolution medium.

Paddle type

Paddle method can be used for floating formulations and those formulations that don't float even after swelling. The dissolution apparatus consists of a cylindrical vessel made of glass or inert transparent material. The volume of the vessel generally used was 900ml.In the vessel dissolution media was taken and the formulation to be evaluated had to be placed in it. A shaft is present which is connected at one end to a motor and the other end to a basket or paddle according to the method employed.

For basket method unless otherwise specified 40 mesh size for the basket was used. The rpm of the shaft was 100 rpm for basket method and 50 rpm for paddle method .In regular intervals of time samples were withdrawn from the vessel and analyzed for the drug release up to each interval by UV visible spectrophotometer. After withdrawing the sample it is replaced with same amount of dissolution medium to maintain sink conditions.

8.1 Dissolution for Amlodipine[54]

Medium   : 900ml 0.01M Hydrochloric acid

RPM   : 75 rpm 45 Minutes

Time   : 5, 10,15,30,45Minutes

Apparatus: paddle

Temparature: 37^0c $\pm 0.5^0$C

Preparation of 0.01M Hydrochloric acid dissolution medium

5.1 ml Hydrochloric acid in 6 lit water and stirr well to produce 0.01M Hydrochloric acid

Procedure for dissolution

Place the tablet in 6 bowls containing 900ml 0.01M Hydrochloric acid media that has been equillibriated to 37^0C±0.5.Take care to exclude the air bubble of the surface of the tablet.Withdraw the suitable volume of the medium and filter.Measure the absorbance of the filtered solution, at a maximum about 239 nm.Calculate the content of $C_{20}H_{25}ClN_2O_5$ in the medium from the absorbance obtained from a solution of known concentration of Amlodipine besilate *RS* in the same medium.Not less than 70% of the stated amount of $C_{20}H_{25}ClN_2O_5$.

Calculation:

$$\frac{E_{max} \text{ of standard} \times 100}{E_{max} \text{ of   test}}$$

9. DRUG CONTENT

Chromatographic conditions

 Coloumn:A stainless steel column 15cm×3.9mm. packed with octadecylsilane bonded to porous silica

   Flow rate: 1 ml per minute

   Wave length : 237 nm

   Injection volume: 10µl

   Run time: 12.30 minutes

Mobile phase:-

           A mixture of 15 volume of acetonitrile,35 volume of methanol and 50 volume of a solution prepared by dissolving 7.0 ml of triethylamine in 1000ml of water,adjusted to p^H 3.0 with phosphoric acid.

Test solution (A):-Weigh and powder 20 tablets.Weigh a quantity of the powder containing 50 mg of amlodipine,dissolve in the mobile phase,dilute to 50.0ml with the mobile phase and centrifuge.

Test solution(B):-Dilute 5 ml of test solution A to 100.0 ml with the mobile phase.

Reference solution(A):-A solution of Amlodipine besilate *RS* containing 0.005 prcent w/v of amlodipine in the mobile phase.

Reference solution (B):-Dilute 5ml of test solution (A) to 100.0ml with mobile phase.Dilute 5.0 mlof this solution to 50.0 ml with mobile phase.

Reference solution(C):-Dissolve 5mg of Amlodipine besilate *RS* in 5ml of strong hydrogen peroxide solution.Heat at 70^0C for 45 minutes and centrifuge.

Procedure:-Inject 10µl mobile phase ,test solution,reference solution in to chromatograph .Record the chromatograms ,and measure the response for major peaks.

Calculate % release of Amlodipine using the below equation

Calculation:-

% of Amlodipine

$$\frac{TA}{SA} \times \frac{SW}{TW} \times \frac{SP}{100} \times 0.7213 \times \text{Average weight}$$

Where,

TA= Peak area due to Amlodipine in sample preparation

SA= Peak area due to Amlodipine in standard preparation

SW= Weight of standard

TW= Weight of test

SP= Purity of standard

10. Disintegration Time[55,56]

      Randomly selected six tablets from each batch and disintegration performed in disintegration apparatus(Veego,Mumbai) at 37 ± 0.5^0C. To test for disintegration time, one tablet is placed in each tube, and the basket rack is positioned in a one liter beaker of water, simulated gastric fluid or simulated intestinal fluid at body temperature such that the tablet remain 2.5 cm below the surface of the liquid on their upward movement and descend not closer than 2.5 cm from the bottom of beaker. A standard motor device is use to move the basket assembly containing the tablet up and down through a distance of 5-6 cm at a frequency of 28-32 cycles per minute. To be in compliance with standards the tablets must disintegrate and all the particles must pass through 10 mesh sieve in the time specified.

TableNo.27specifications for disintegration time for tablets

Uncoated tablets	NMT15 min in water with disc $37^0c\pm2^0c$
Coated tablets	NMT 30 min in water with disc for film coated tablets and NMT 60 min for other than film coated tablets.
Enteric coated	Intact for 1 hr in 0.01N HCL&disintegrate within 2 hr in Mixed phosphate buffer .
Dispersible/Soluble	Within 3 min in water at $25^0c\pm1^0c$
Orodispersible	Within 1 min
Effervescent	5min in 250 ml water at 20-30^0c
Buccal and sublingual	Not applicable but dissolve within 15-30 min

B) DRUG EXCIPIENT COMPATIBILITY STUDIES

The compatibility of drug and formulation components are important perquisite before formulation.It is therefore necessary to confirm that the drug does not react with the polymers and excipients.under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulations.

Procedure:

Drug mixed with excipients in different ratio. These mixtures were kept in a 5ml glass white colored vials and packed properly. These vials are exposed to room temperature and $25^0C/60\%RH$& $40^0C/75\%RH$.2-3 gm of blend was prepared which was filled in 3 vials. Observation for physical appearance were made at zero weeks,1 month, the samples were withdrawn for analysis of appearance,moisture content,assay& related substance.

7. RESULTS AND DISCUSSION

7.1) PHYSIOCHEMICAL PARAMETERS

1.DESCRIPTION

Table no:28

SL NO	DESCRIPTION AMLODIPINE	RESULTS
1	COLOUR	White crystalline powder
2	ODOUR	Odourless
3	TASTE	Tasteless

2. SOLUBILITY

Table no:29

RAW MATERIAL(API)	RESULTS
AMLODIPINE	Water:- Slightly soluble Methanol:- Freely soluble Ethanol:- Sparingly soluble 2-Propanol:-Slightly soluble

3. p^H ANALYSIS

Table No:30

RAW MATERIAL(API)	RESULT
AMLODIPINE	1-6 at 37^0C

4. MELTING POINT

Table no: 31   Melting point

RAW MATERIAL(API)	MELTING POINT
AMLODIPINE	178-179^{0}C

5. CHEMICAL NATURE

Table no:32 Amlodipine specification

S.NO	PARAMETERS	AMLODIPINE
1	Molecular formula	$C_{20}H_{25}ClN_2O_5$
2	Molecular weight	408.879g/mol
3	IUPAC name	3-ethyl 5-methyl 2-[(2-aminoethoxy]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5dicarboxylate
4	Chemical nature	Long acting 1,4 dihydropyridine calcium channel blocker,Antianginal,Antihypertensive

6.HYGROSCOPICITY

Table no:33 Interpretation of results based on percent increase in mass

RAW MATERIAL(API)	RESULT
Amlodipine	Non hygroscopic

7. PARTICLE SIZE ANALYSIS (sieve analysis)

Table No:34 sieve analysis

RAW MATERIAL(API)	NATURE OF SAMPLE
AMLODIPINE	Fine powder

8. FLOW PROPERTY MEASUREMENT

- **ANGLE OF REPOSE**

Table no:35 Flow property and corresponding Angle of repose

RAW MATERIAL(API)	ANGLE OF REPOSE	FLOW PROPERTY
AMLODIPINE	34.90^0	Good

- **DENSITY**

- ❖ **BULK DENSITY**

Table no:36 Bulk density

RAW MATERIAL(API)	BULK DENSITY g/ml
AMLODIPINE	0.625

❖ **TAPPED DENSITY**

Table No:37 Tapped density

RAW MATERIAL(API)	TAPPED DENSITY (g/ml)
AMLODIPINE	0.714

❖ **COMPRESSIBILITY INDEX**

Table No:38 Compressibility Index and corresponding flow property

RAWMATERIAL (API)	COMPRESSIBILITY INDEX	FLOW PROPERTY
AMLODIPINE	12.46	Good

❖ **HAUSNER'S RATIO**

Table No:39 Hausner's ratio

RAW MATERIAL (API)	HAUSNER'S RATIO	FLOW PROPRTY
AMLODIPINE	1.1424	Good

9. DRUG CONTENT

Table No:40 Drug content

RAW MATERIALS(API)	ASSAY (%)
AMLODIPINE	103.39%

7.2 COMPATIBILITY STUDIES

Table No:41 Compatibility studies of Amlodipine with excipients

Drug	Excipients	1st day	1st week	2nd week	3rd week
	(Ratio=1:1)	40^0 C & 75% RH	40^0 C&75% RH	40^0C&75% RH	40^0C&75% RH
AMLODIPINE	Starch	Nd	Nd	Nd	Nd
	Sodium starch glycolate	Nd	Nd	Nd	Nd
	Magnesium stearate	Nd	Nd	Nd	Nd
	Talc	Nd	Nd	Nd	Nd
	Lactose	Nd	Nd	Nd	Nd
	Methyl paraben	Nd	Nd	Nd	Nd
	Propyl paraben	Nd	Nd	Nd	Nd

Where,

RH= Relative humidity

Nd= change not detectable

FT-IR SPECTRA OF AMLODIPINE

Figure No:5 FT-IR spectra of pure drug Amlodipine

FT-IR SPECTRA OF AMLODIPINE+ SSG

Figure No:6 FT-IR spectra of Amlodipine+SSG

Kerala State Drug Pharmaceutical Limited

Sample Name : Amlodipine
Division   : QC
Creation Date : 16/3/2016
Data array type : Linear data array
Horizontal   : Wave number[cm-1]
Vertical   : % Transmittance
Acquired by   : Analyst
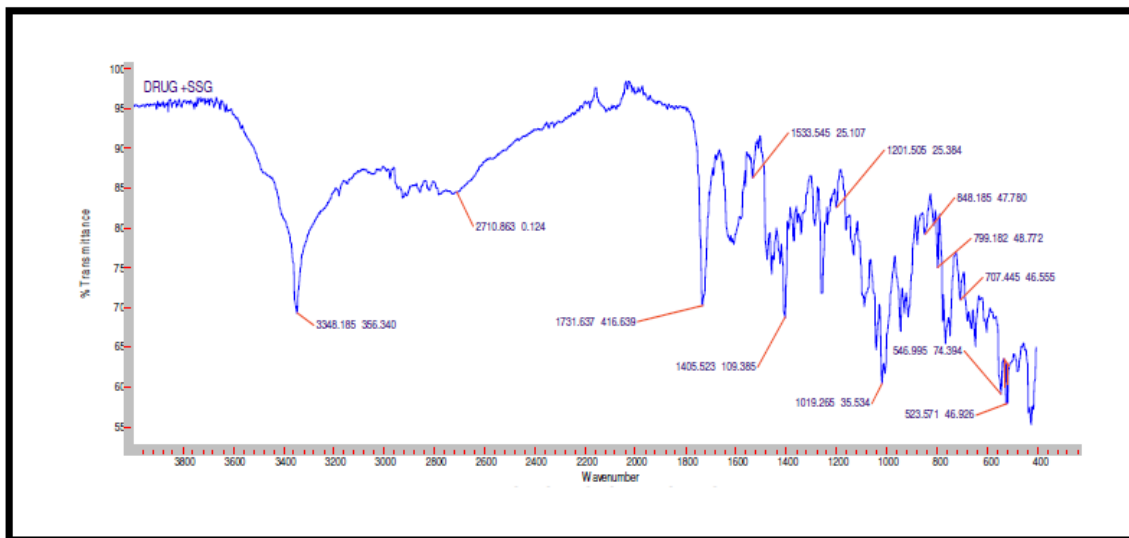
FT-IR SPECTRA OF OPTIMIZED FORMULATION

Figure No:7 FT-IR spectra of optimized formulation

Kerala State Drugs Pharmaceutical Limited

Sample Name : Amlodipine with exicipients
Division   : QC
Creation Date : 16/3/2016
Data array type : Linear data array
Horizontal   : Wave number[cm-1]
Vertical   :   % Transmittance
Acquired by   : Analyst

INFERENCE: Spectrum of pure drug Amlodipine compared with spectrum of Amlodipine with excipients.The disappearance or shifting of Amlodipine peak in any of the spectra studied.There is no interference to the drug and excipients.

7.3 RESULTS AND DISCUSSION

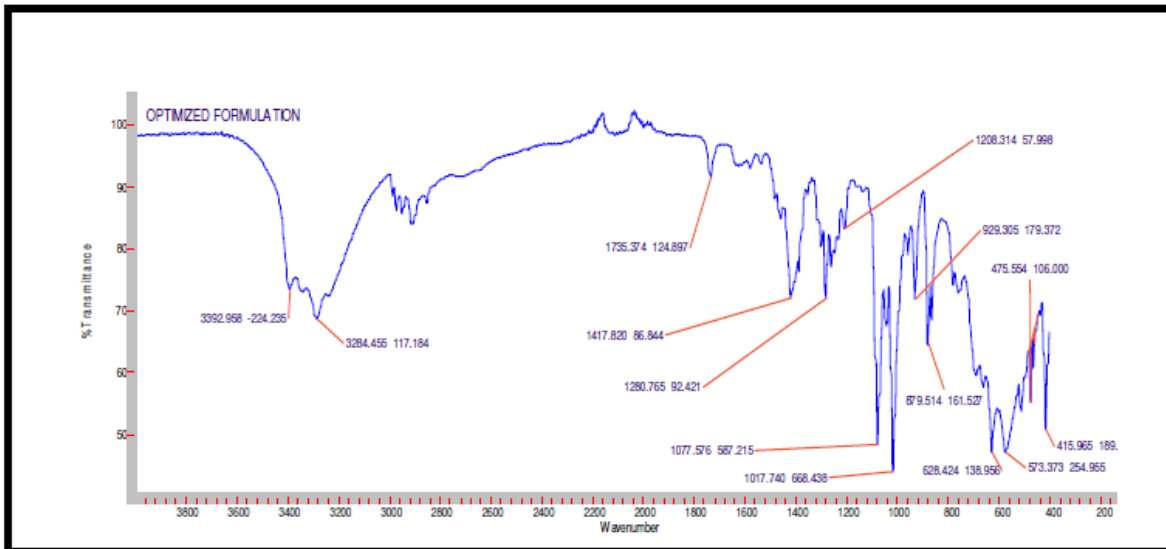**Table No:42** Precompression parameters of Amlodipine granules trials:

Formulations	Bulk density (gm/cm$^{2)}$	Tapped density (gm/cm^2)	C.I (%)	Angle of repose(^{0})	H.R	Moisture content
F_1	0.42	0.54	32.22	$42^0.21^{'}$	1.383	0.0352
F_2	0.49	0.50	20.00	$38^0.65^{'}$	1.222	0.0311
F_3	0.48	0.55	18.15	$36^0.23^{'}$	1.25	0.0219
F_4	0.41	0.51	28.33	$47^0.32^{'}$	1.42	0.0310
F_5	0.43	0.52	27.3	$48^0.26^{'}$	1.382	0.030
F_6	0.41	0.51	29.61	$46^0.56^{'}$	1.255	0.0217
F_7	0.45	0.55	18.18	$31^0.63^{'}$	1.125	0.0219
F_8	0.47	0.55	20.0	$30^0.23^{'}$	1.25	0.0214
F_9	0.48	0.51	15.69	$28^0.13^{'}$	1.146	0.0216

Inference: Formulations F_1 to F_3 has showing the significant flow property,angle of repose and Hausner's ratio because of the inclusion of magnesium stearate and lactose,and in case of F4-F6 has indicating the high Angle of repose due to the poor flow property in the absence of magnesium stearate lubricant.F7-F9 shown good flow as indicated by angle of repose and Hausner's ratio because of increase in concentration of lubricant magnesium stearate.(Magnesium stearate filled the cavities of lactose and this selective adhesion improves the flowability of the powder)

7.4 POST COMPRESSION PARAMETERS OF AMLODIPINE TABLETS

Table No:43 Post compression parameters of Amlodipine tablets

Formulations	Weight variations (mg)	Hardness (kg/cm^2)	Thickness (mm)	Disintegration Time(min)	Friability (%)
F_1	106-113	4.8	3.64	23	0.069
F_2	110-120	5	3.43	25	0.059
F_3	101-112	4.6	3.72	24	0.068
F_4	98-105	4.2	3.84	20	0.059
F_5	112-120	5.1	3.44	22	0.062
F_6	114-120	4.7	3.41	21	0.005
F_7	108-119	4.3	3.39	20	0.056
F_8	109-121	4.4	3.12	18	0.052
F_9	115-118	4.1	3.40	15	0.050

7.5 DRUG CONTENT

Table No:44 Drug Content Values of Amlodipine

FORMULATION	AMLODIPINE
F_6	93.21
F_7	97.54
F_8	98.79
F_9	103.39

Calculation of drug content value of Amlodipine in F9

Drug content :-Area of sample × weight of standard × Assay of standard×0.7213×110.33

Area of standard   weight of sample   100

Area of sample=3282559

Area of standard=2388483

Weight of standard=52.28mg

Weight of sample= 1102.50mg

Assay of standard=99.68%

Drug content : $\dfrac{3282559}{2388483}$ × $\dfrac{52.28}{1102.50}$ × $\dfrac{99.68}{100}$ × 0.7213 × 110.33

= 103.39 of LC

HPLC CHROMATOGRAM OF AMLODIPINE WITH STANDARD

Figure No:8 HPLC chromatogram of Amlodipine standard

Acquired by   : Analyst
Sample Name   : Amlodipine Tabs.lp
Sample ID   : Standard
Injection Volume   : 20 uL
Data Filename   : 11.03.amlo.2.lcd

Chromatogram
Amlodipine Tabs.lp C:\LabSolutions\Data-2014\AMLODIPINE\11.03.amlo.2.lcd

PeakTable

Detector A Ch1 237nm

Peak#	Ret. Time	Area	Height	Area %	Conc.	Theoretical Plates/meter	Tailing Factor
1	1.817	2836	95	0.116	0.000	0.000	0.000
2	2.422	36081	3027	1.470	0.000	6591.254	0.774
3	2.779	14653	686	0.597	0.000	3401.753	1.945
4	3.292	7253	809	0.295	0.000	328.575	0.000
5	3.492	9038	795	0.368	0.000	67.843	0.000
6	3.620	10299	775	0.419	0.000	85.927	0.000
7	4.317	2375103	217938	96.735	0.000	24166.723	0.942
Total		2455264	224124	100.000			

Figure No:9 HPLC chromatogram of sample drug Amlodipine

Acquired by   : Analyst
Sample Name   : Amlodipine Tabs.Ip
Sample ID   : B#QCTD03160239
Injection Volume : 20 uL
Data Filename   : 11.03.amlo.4.lcd

Chromatogram
Amlodipine Tabs.Ip C:\LabSolutions\Data-2014\AMLODIPINE\11.03.amlo.4.lcd

PeakTable

Detector A Ch1 237nm

Peak#	Ret. Time	Area	Height	Area %	Conc.	Theoretical Plates/meter	Tailing Factor
1	2.241	81372	9642	2.202	0.002	10353.255	0.000
2	2.417	34685	3943	0.938	0.000	974.934	0.000
3	2.786	69282	7821	1.875	0.000	17309.952	0.000
4	3.275	4716	739	0.128	0.000	226.253	0.000
5	3.561	199795	12925	5.406	0.000	8452.809	0.000
6	4.330	3285197	302431	88.886	0.000	24295.191	0.954
7	5.309	13942	419	0.377	0.000	2670.404	0.000
8	6.656	2494	170	0.067	0.000	29961.804	0.875
9	8.067	4488	228	0.121	0.000	23914.841	0.870
Total		3695970	338318	100.000			

7.6 POST COMPRESSION PARAMETERS OF AMLODIPINE INNOVATOR

Table No.45 Post compression parameters of Amlodipine innovator

SL.NO	PARAMETERS	INNOVATOR (Amlong)
1	Weight variation	109-117mg
2	Hardness	$3.8Kg/cm^2$
3	Thickness	3.5mm
4	Friability	0.059%
5	Disintegration time	12min

7.7 DRUG RELEASE

7.7.1. INNOVATOR DRUG RELEASE PROFILE

Table No:46 Innovator drug release profile

TIME(MIN)	INNOVATOR (AMLONG)
5	72.4%
10	84.2%
15	93.7%
30	96.8%
45	98.2%

7.7.2 DRUG RELEASE VALUE OF AMLODIPINE

**Table No:47** Percentage Drug release value of Amlodipine

FORMULATIONS	% Drug release of Amlodipine at 45 minutes
F_1	80.07%
F_2	82.68%
F_3	84.72%
F_4	84.93%
F_5	87.48%
F_6	89.50%
F_7	92.37%
F_8	94.53%
F_9	96.87%

7.7.3 RELEASE PROFILE OF AMLODIPINE IN F6 COMPARED WITH INNOVATOR

Table No:48 comparative release of amlodipine from innovator and F_6

Time	%Release of innovator	% Release from F_6
5	72.4	58.29
10	84.2	62.72
15	93.7	69.54
30	96.8	79.23
45	98.2	89.50

Figure No: 10 Release profile of Amlodipine in F_6 compared with innovator
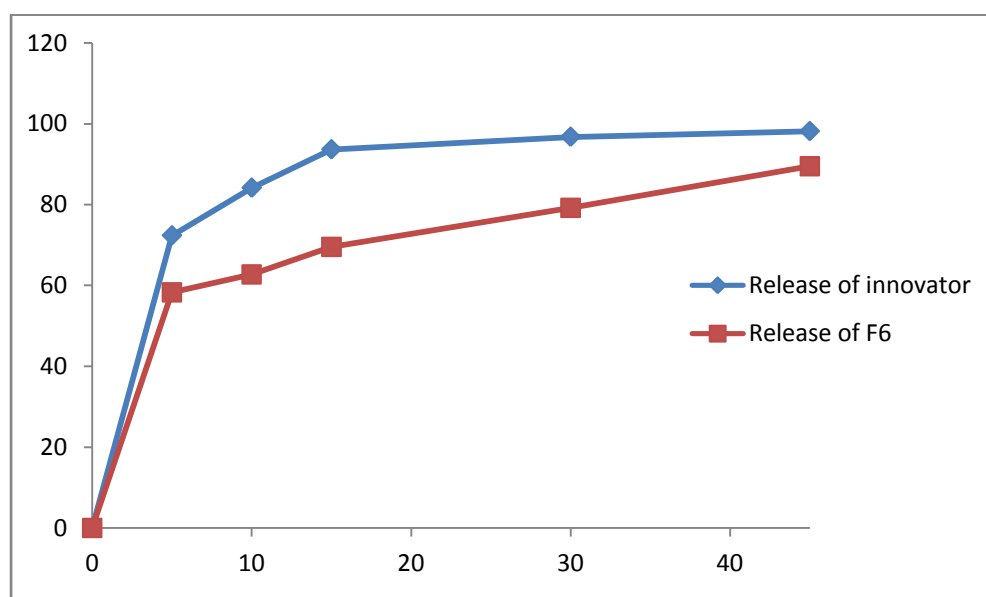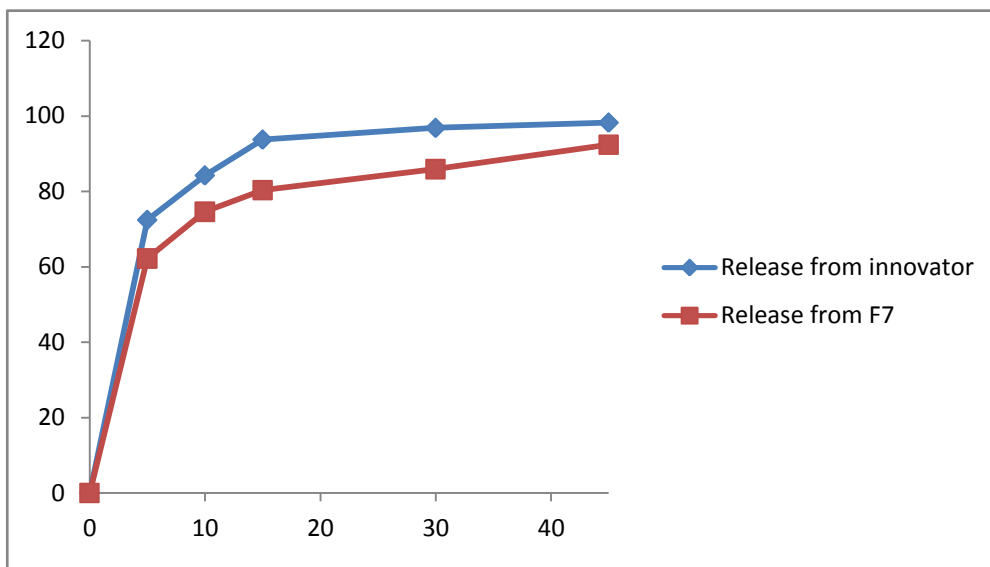

Inference: The release profile of the Amlodipine from F6 was less than compared to innovator at the end of 45 minutes

7.7.4 RELEASE PROFILE OF AMLODIPINE IN F_7 COMPARED WITH INNOVATOR

Table No:49 Comparative release of Amlodipine from innovator and F_7

Time(min)	% Release of innovator	% Release from F_7
5	72.4	62.2
10	84.2	74.6
15	93.7	80.3
30	96.8	85.9
45	98.2	92.37

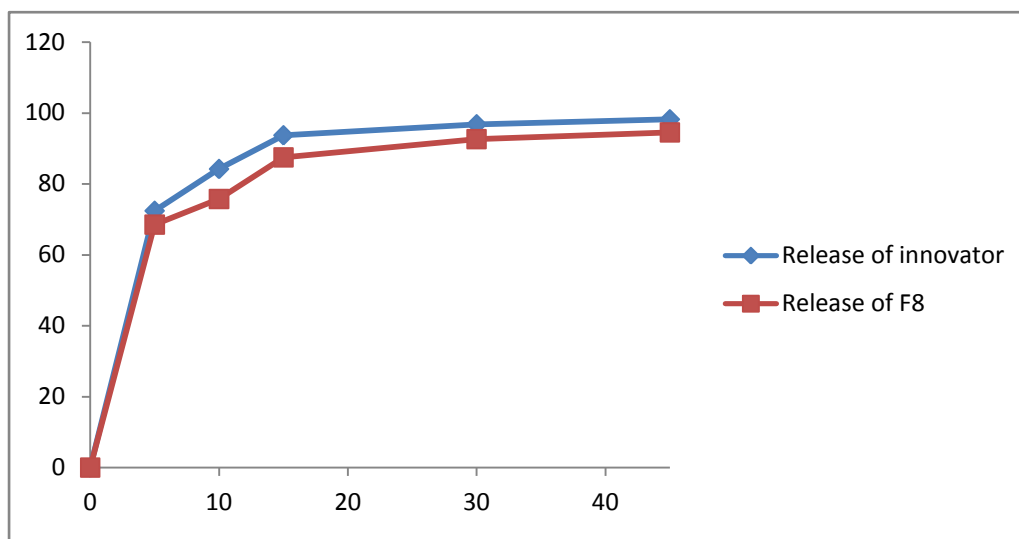**Figure No. 11** Release profile of Amlodipine in F_7 compared with innovator

Inference: The release profile of Amlodipine from F7 was compared to innovator and the release rate was less than the innovator at the end of 45 minutes

7.7.5 RELEASE PROFILE OF AMLODIPINE IN F$_8$ COMPARED WITH

THE INNOVATOR

Table No:50 Comparative release of Amlodipine from innovator and F$_8$

Time(min)	% Release of innovator	%Release from F$_8$
5	72.4	68.53
10	84.2	75.76
15	93.7	87.47
30	96.8	92.64
45	98.2	94.53

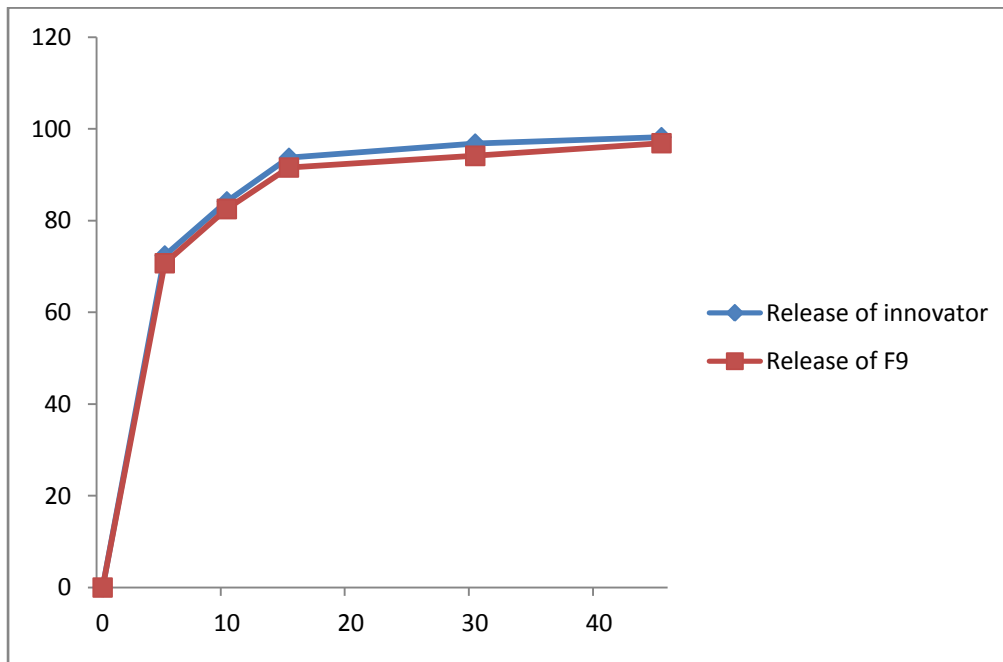**Figure No.12** Release profile of Amlodipine in F$_8$ compared with the innovator

Inference: The release profile of Amlodipine from F$_8$ was compared with the innovator and the release was compatable to that of innovator at the end of 45 minutes

7.7.6 RELEASE PROFILE OF AMLODIPINE FROM F₉ COMPARED WITH INNOVATOR

Table No:51 Comparative release of Amlodipine from innovator and F_9

Time(min)	%Release of innovator	% Release from F_9
5	72.4	70.69
10	84.2	82.53
15	93.7	91.59
30	96.8	94.12
45	98.2	96.87

Figure No.13 Release profile of Amlodipine from F_9 compared with innovator

Inference: The release profile of Amlodipine from the F9 was compared with the innovator and the release was almost equal and compatable with innovator at the end of 45 minutes.

7.7.7 COMPARISON OF DISSOLUTION PROFILE OF FORMULATIONS WITH INNOVATOR

Table No: 52 Comparison of dissolution profile of Amlodipine formulations with innovator

Time (min)	Innovator % Release	% Drug Release			
		F_6	F_7	F_8	F_9
5	72.4	58.29	62.2	68.53	70.69
10	84.2	62.72	74.6	75.76	82.53
15	93.7	69.54	80.3	87.47	91.59
30	96.8	79.23	85.9	92.34	94.12
45	98.2	89.5	92.37	94.53	96.87

7.7.8 COMPARITIVE RELEASE PROFILE OF AMLODIPINE IN VARIOUS FORMULATIONS WITH INNOVATOR

Figure No: **14** Comparative release profile of Amlodipine in various formulations with innovator
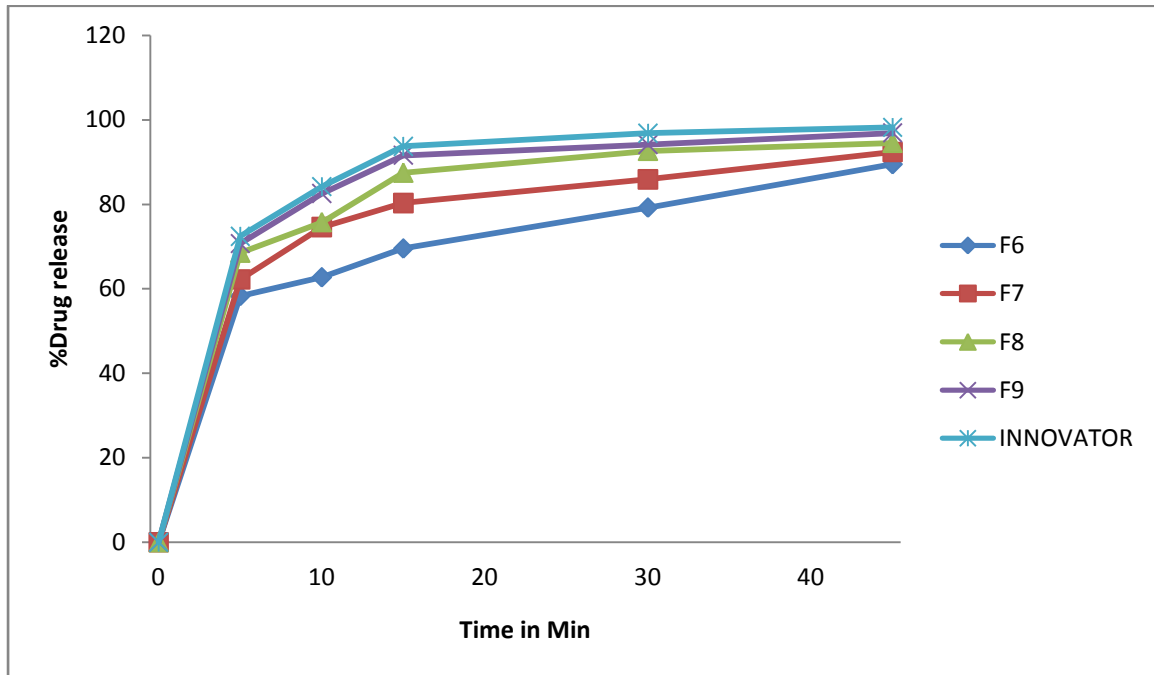
Inference: Comparative release profile of Amlodipine from various formulations showing the release from the F9 matching with the innovator

7.8 STABILITY STUDY

7.8.1 STABILITY DATAS FOR OPTIMIZED FORMULATIONS AT 25⁰C&60%RH FOR AMLODIPINE IMMEDIATE RELEASE TABLETS

Table No: 53 stability data for optimized formulations at 25^0C & 60% RH for Amlodipine immediate release tablet IP 5mg

S.NO	PARAMETERS	STORAGE CONDITIONS (25^0 C& 60% RH)		
		INITIAL	30 DAYS	45 DAYS
1	Description	Orange colored ,round shaped	N.D	N.D
2	Weight variation	115-118	Within limits	Within limits
3	Hardness	4.4	4.4	4.2
4	Thickness	3.4	3.4	3.4
5	Friability	0.052	0.054	0.059
6	Disintegration time	15	15	15
7	Drug release	96.8%	96.%	96%
8	Drug content	103.39	102.75	102.62
9	Moisture content	0.0216	0.0219	0.0321

7.7.2 STABILITY DATA FOR OPTIMIZED FORMULATIONS AT 40^{0}C &75%RH FOR AMLODIPINE IMMEDIATE RELEASE TABLETS

Table No: 54 stability data for optimized formulations at 40^{0}C & 75% RH for Amlodipine immediate release tablet IP 5mg

S.NO	PARAMETERS	STORAGE CONDITIONS (40^0 C& 75% RH)		
		INITIAL	30 DAYS	45 DAYS
1	Description	Orange coloured ,round shaped	N.D	N.D
2	Weight variation	115-118	Within limits	Within limits
3	Hardness	4.4	4.4	4.2
4	Thickness	3.4	3.4	3.4
5	Friability	0.052	0.055	0.059
6	Disintegration time	15	15	15
7	Drug release	96.8%	96.82%	96.74%
8	Drug content	103.39	103.35	101.95
9	Moisture content	0.0216	0.0219	0.0231

Table No:55 Drug release of Amlodipine at 25^0C & 60% RH

DRUG	% Drug release		
	Initial	30 days	45 days
Amlodipine	96.8	96.78	96.75

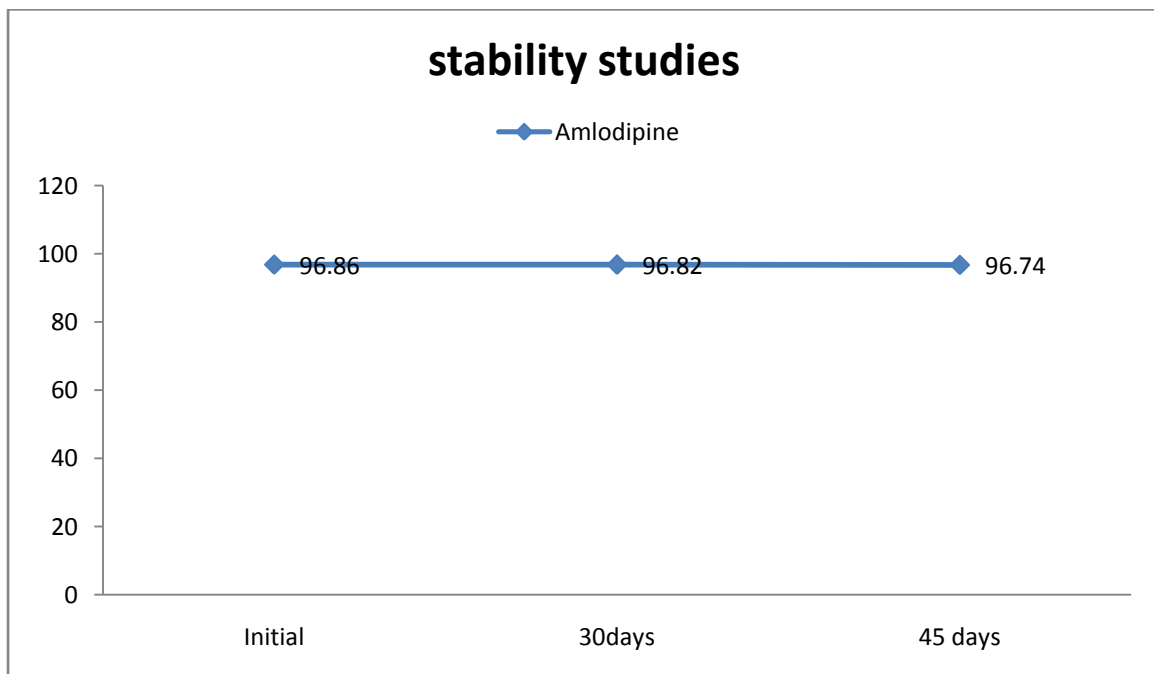**Figure No:15** Drug release of Amlodipine at 25^0C&60%RH
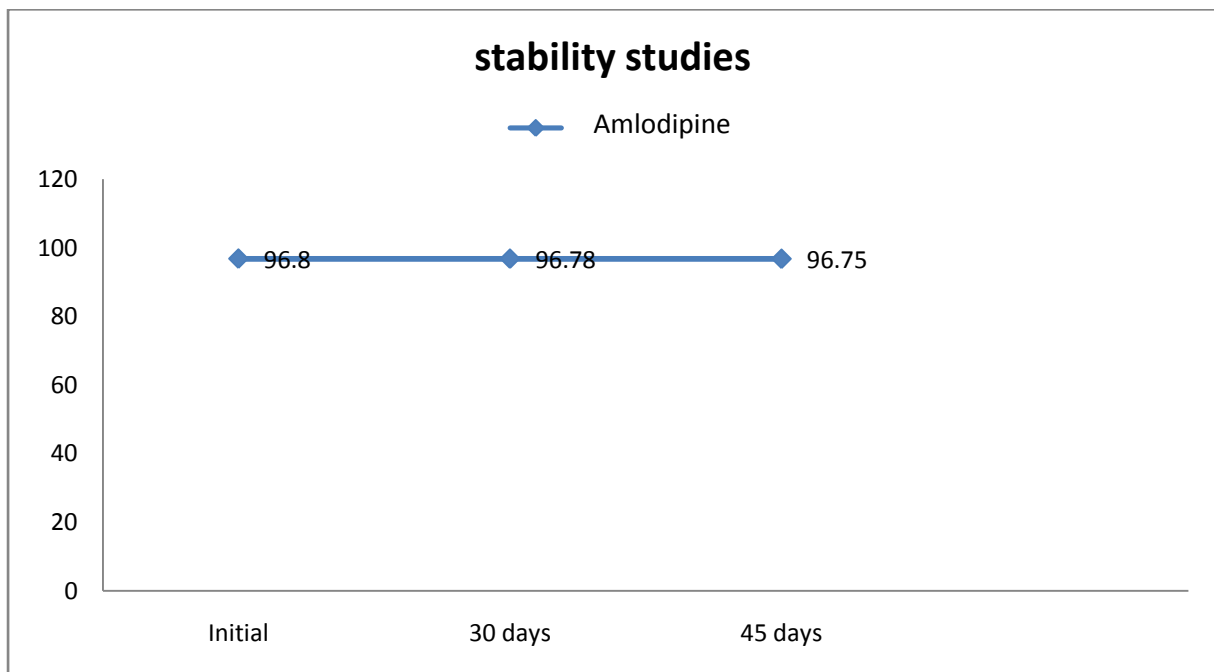
Inference: The drug release was not significantly reduced at the end of 30 days and 45 days storage at 25^0C &60%RH indicating stability of the formulation.All parameters are within the specified limits at the end of the storage.

Table No:56 Drug release of Amlodipine at 40^0C & 75% RH

DRUG	% Drug release		
	Initial	30 days	45 days
Amlodipine	96.86	96.82	96.74

Figure No. 16 Drug release of Amlodipine at 40^0C & 75% RH

Inference: The drug release was not significantly reduced at the end of 30 days and 45 days storage at 40^0C &75%RH indicating stability of the formulation.All parameters are within the specified limits at the end of the storage.

8. SUMMARY AND CONCLUSION

Totally 9 (n=9) formulations were prepared with Amlodipine granules ,prepared separately in a MCG mixer.

Pre compression parameters like Bulk density , Tapped density ,Angle of repose indicate all formulation show good flow properties.

Tablets are compressed using CADMACH compression machine and tablets are evaluated for post compression parameters like Weight variation,Hardness,Friability,Disintegration and Dissolution parameters.

Formulation F1-F6 does not meet the criteria for hardness and disintegration time due to the improper mixing of lubricant,disintegrant and binder with dry mixture.

Formulations F7-F9 has shown post compression within specified limits of the innovator.The release profile of the formulations F7-F9 was compared with innovator and all the formulations has shown a release of 70-95% and formulation F9(Amlodipine=7mg ,Starch=55mg ,Sodium starch glycolate=3mg,Magnesium Stearate=3mg,Lactose=26.4mg ,Talc=5mg ,Methyl paraben=0.5mg ,Propylparaben= 0.1mg ,Coloring material(sunset yellow)= 0.005mg) has matched the innovator release profile.F9 has 96.87% Drug release.

The compressed tablets packed in blisters and subjected to stability studies at 40^0C and 75% RH samples were analyzed at regular intervals as mentioned in stability protocol,and found that no significant changes observed in any of the studied parameters during the study period,thus it could be concluded that formulation F9 said to be stable.

From the study, it may concluded that the Amlodipine IP 5mg film coated tablets can be prepared as immediate release formulations compared to conventional dosage forms.

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