"FORMULATION DEVELOPMENT AND EVALUATION OF IMMEDIATE RELEASE DOSAGE FORMS OF ANTI-HYPERTENSIVE AGENT IN COMBINATION"

A Thesis Submitted to

NIRMA UNIVERSITY

In Partial Fulfillment for the Award of the Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

BY

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Under the guidance of

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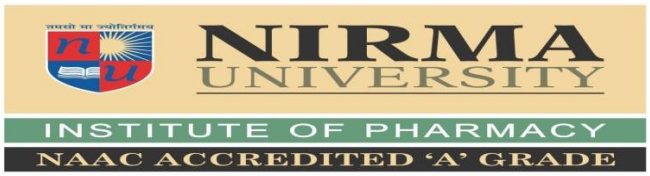

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MAY 2018

CERTIFICATE

This is to certify that the dissertation work entitled "Formulation development and evaluation of Immediate release dosage forms of Anti-hypertensive agent in combination" submitted by Ms. Ankita Singh with Regn. No. (16MPH102) 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 IPCA Laboratories, Silvassa 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.

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A dose of life

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To Whomsoever It May Concern

This is to certify that Ms. Ankita Singh student of Institute of Pharmacy, Nirma University, Ahmedabad. has successfully completed her Training and Project from 20th July, 2017 to 20th January, 2018 in Tech. Service (R&D) in our Organization.

She has attended the training and projects in our organization. During her training and projects period, she was found to be sincere and hard working. Her performance and conduct was found good.

We wish her all success in her future.

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DECLARATION

I hereby declare that the dissertation entitled ""Formulation development and evaluation of Immediate release dosage form of Anti-hypertensive agent in combination" is based on the original work carried out by me under the guidance of Mrs Preeti Dali, Head of Research and Development, Ipca Laboratories, Mumbai and Dr. Tejal Mehta, Professor and Head, Department of Pharmaceutics, Institute of Pharmacy, Nirma University. 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.

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ANKITA SINGH

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Abbreviations

Sr no.	Abbreviations	Full form
1	ARB	Angiotensin Receptor Blocker
2	AT1R	Angiotensin II Type 1 Receptor
3	AT2R	Angiotensin II Type 2 Receptor
4	ACE	Angiotensin Converting Enzyme
5	Avg. Wt	Average Weight
6	API	Active Pharmaceutical Ingredient
7	B.D.	Bulk Density
8	BP	Blood Pressure
9	B.P.	British Pharmacopeia
10	C.I	Compressibility Index
11	DC	Direct Compression
12	DT	Disintegration Time
13	EU	European Union
14	FBD	Fluidized Bed Drier
15	H.R	Hausner's Ratio
16	HDPE	High Density Poly Ethylene
17	IR	Immediate Release
18	IR Spectroscopy	Infra-Red Spectroscopy
19	Kg/cm2	Kilogram/Centimeter
20	KN	Kilo newton
21	KP	Kilo pascal
22	LOD	Loss On Drying
23	Mg	Milligram
24	Mg. Stearate	Magnesium Stearate
25	Mg/tab	Milligram/tablet
26	Min.	Minute
27	Ml	Milliliter
28	MM	Millimeter

29	Ph. Eur.	European Pharmacopeia
30	RAS	Renin Angiotensin System
31	RH	Relative Humidity
32	RMG	Rapid Mixer Granulator
33	RPM	Revolution Per Minute
34	RS	Relative Substances
35	T.D	Tapped Density
36	Total Imp.	Total Impurity
37	USFDA	United Stated Food And Drug Administration
38	USP	United States Pharmacopiea
39	WG	Wet Granulation
40	WHO	World Health Organization
41	XRPD	X-Ray Powder Diffraction

ABSTRACT

Formulation development and evaluation of immediate release dosage form of anti-hypertensive agent in combination.

The aim of the present research was to formulate and develop immediate release dosage form combination for the treatment of hypertension. There were two drugs used of BCS class II and III in combination in this formulation. In this study two formulations were formulated, developed and evaluated. The two approaches used were; one was tablet and other was pellets. Tablets are considered as one of the most important route for administration of drug in case of immediate release formulation. Tablet as a dosage form offers a wide range of advantages as compared to other route of administration. Tablet is consider as first choice among all dosage forms because of its expediency of self administration, compactness and trouble-free manufacturing; low cost and non-invasive therapy etc. Immediate release formulation disintegrates rapidly subsequent to administration with improved rate of dissolution. In formulation of tablets wet granulation method was used to prepare the tablets by using different excipient lactose monohydrate, pregelatinized starch maleic Acid, iron oxide yellow, dried maize starch, Sodium steary fumarate and Magnesium stearate. Preformuation study was performed in order to check the compatibility of drug and excipient. Pre-compression and post compression parameter like bulk density, hardness and dissolution were performed to ensure that the formulation was of maintained standard and identical with the innovator produtct. The other method to formulate immediate release formulation was pellets. Pellets are multiparticulate dosage form which was formed by the agglomeration of fine powdered excipient and drugs together that leads to the formation of small free flowing spherical or semi spherical particles. This technique is called as pelletization process. Pellets are typically varied between 500-1500 µm in size for pharmaceutical applications. It is of great interest over other similar techniques due to its uniformity of dose, less susceptibility of dose dumping, less friability etc. The formulation of pellets was done by using extruder spheronized as technique with the help of excipents like microcrystalline cellulose, polyvinylpyrolidone and crosspovidone. In this study the process parameter like speed of spheronizer and formulation parameter like quantity of disintegrating agent were optimized. The evaluation of pellets was done on the bases of friability, shape and dissolution.

CONTENT

CHAPTER 1

INTRODUCTION

INTRODUCTION

1.1 INTRODUCTION TO HYPERTENSION

1.1.1 OVERVEIW OF HYPERTENSION(Nandhini, 2014)

"Hypertension can be determined as either a constant systolic blood pressure of greater than 140 mm Hg or a constant diastolic blood pressure of greater than 90 mm Hg."

Hypertension consequences from increased peripheral vascular smooth muscle tone, causes increase in arteriolar resistance and reduced capacitance of venous system.

Chronic hypertension, either systolic or diastolic is capable of producing congestive heart failure, myocardial infarction, renal damage and cerebrovascular accidents.

The occurrence of morbidity and mortality considerably reduced when hypertension is detected early and is properly treated.

The categories of hypertension are:-

Stages of hypertension	Systolic blood pressure (SBP)	Diastolic blood pressure(DBP)
Normal	<120 mm Hg	<80 mm Hg
Prehypertension	120-139 mm Hg	80-89 mm Hg
Stage 1 hypertension	140-159 mm Hg	90-99 mm Hg
Stage 2 hypertension	>160 mm Hg	>100 mm Hg

Table 1.1 category of hypertension

1.1.2 ETIOLOGY OF HYPERTENSION(Nandhini, 2014)

Even though hypertension is caused as resulting additional of other disorder process, greater than 90% of patients are suffering from hypertension, a disease of unidentified source affecting the blood pressure regulatory mechanism.

Etiological factors that causes hypertension are

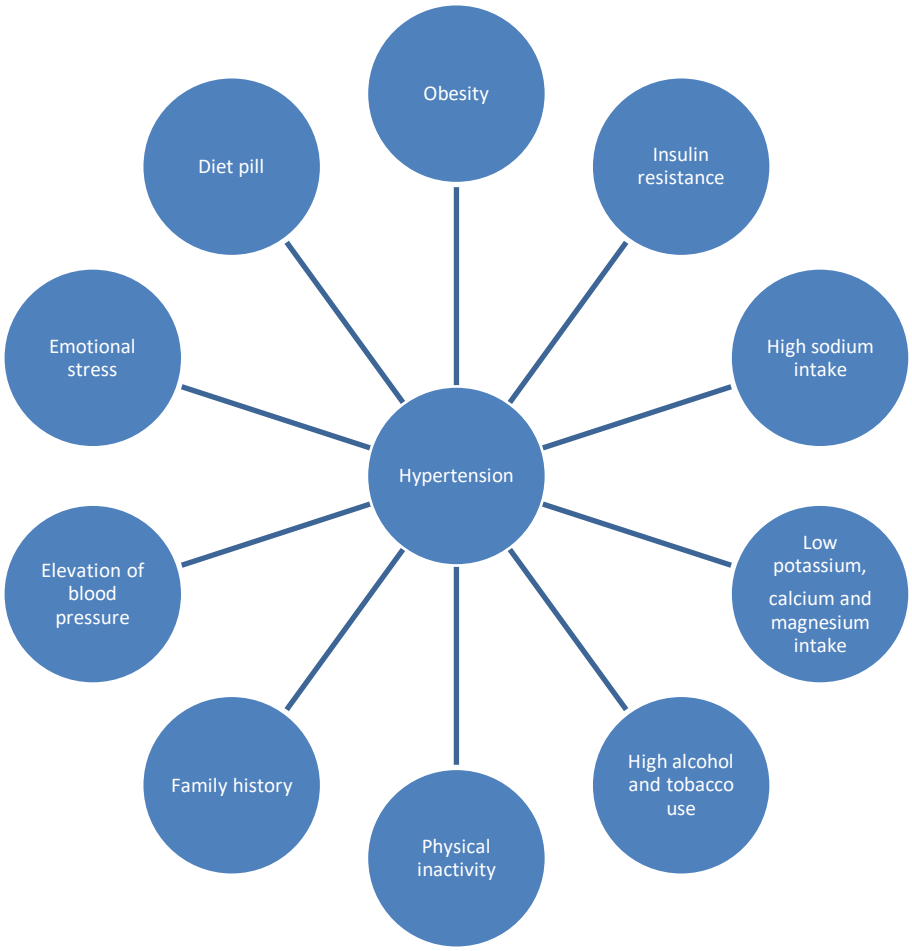


Figure 1.1 Etiological factors of hypertension.

1.1.3 MECHANISMS OF CONTROLLING BLOOD PRESSURE(Gradman, Basile, Carter, & Bakris, 2010)

There are mainly two type of mechanism through which the blood pressure can be controlled

Bororecptors and Sympathetic nervous system

Bororeflexes involving the sympathetic nervous system are responsible for the rapid, moment to moment regulation of blood pressure. A fall in blood pressure causes pressure sensitive neuron to send impulse to the cardiovascular center in the spinal cord.

This prompts a reflex response of increasing sympathetic and decrease in parasympathetic output to heart and vasculature, resulting in vasoconstriction and increase in cardiac output. This results in a compensatory rise in the blood pressure.

Renin –angiotensin –aldosteron system

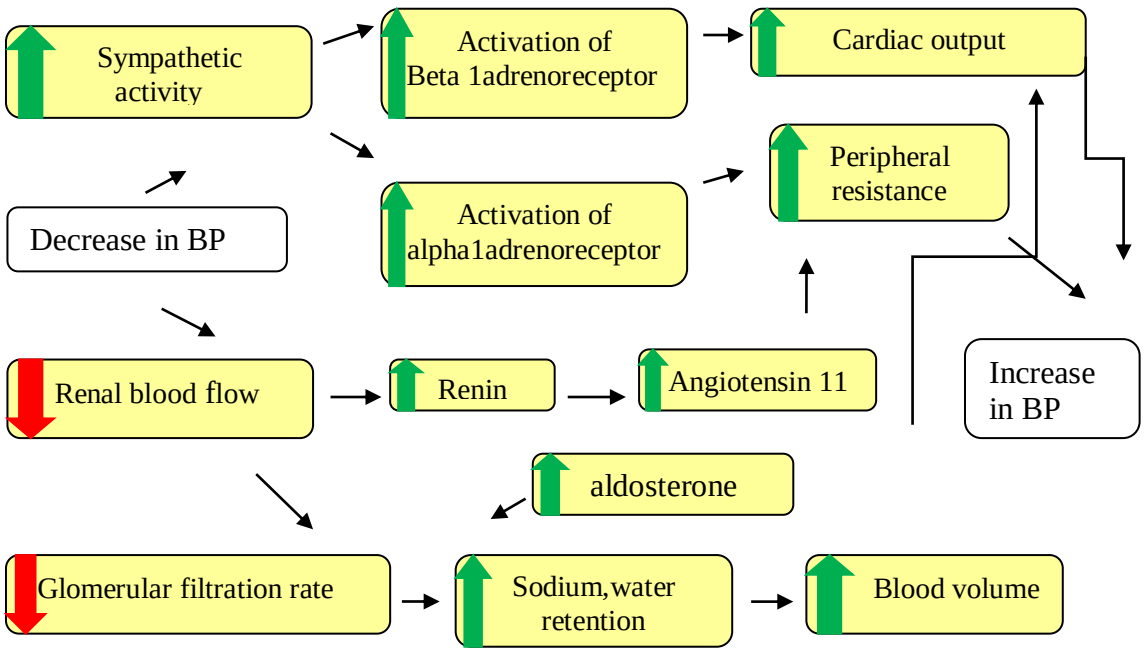
The kidney provides for long term control of blood pressure by altering the blood volume. Bororeceptors in kidney respond to the reduced arterial pressure by releasing enzyme renin.

This peptidase converts angiotensin to angiotensin I, which is converted in angiotensin II in presence of angiotensin converting enzyme (ACE).

Angiotensin is the body's most potent circulating vasoconstrictor, causing an increase in blood pressure.

Furthermore, angiotensin II stimulates aldosterone secretion, leading to increase renal sodium reabsorption and increased blood volume, which contributes to further increase in blood pressure.

Fig 1.2 Response of rennin angiotensin system



1.1.4 TREATMENT APPROACHES

There are number of agents available to treat patient with hypertension. These drugs can be administered as a single agent or as a part of multidrug combination regimen. Following are the major class of antihypertensive agents used in the treatment of hypertension

1. Diuretics
2. ACE inhibitors
3. Calcium channel blockers
4. Beta-blockers
5. Vasodilators
6. Angiotensin receptor inhibitors

1.2 INTRODUCTION TO FIX DOSE COMBINATION THERAPY

(Sica, 2004)(Arora et al., 2015)

Combination therapy is most widely used for the patients in whom achieving the decrease in blood pressure with mono-drug therapy is not possible.

Combination of drug therapy was categorized in two ways

1. Different drug used separately.
2. Fix dose combination

The method of using different drug separately was not so well accepted because there where various issues related to patient compliance, various administered.

Where as in fix dose combination different agents of different category having different mechanism of action are formulated in one formulation having fix dose, thus they have a synergist activity and also reduces the number of pills administered per day.

Thus, fix dose combination increases the patient compliance as well as reduced the cost of the formulation.

Theoretical consideration for fix dose combination:-

1. **Efficacy** –when two administered in fix dose combination which are having complimentary effects to each other it is found that such combination may have fivefold increase in lowering the blood pressure when compared to single drug administered.
2. **Tolerability** – In order to achieve high outcome for the administered therapy one of the major issue is to overcome the side effect of the drug. Mostly all antihypertensive agent causes dose dependent side effects. In mono-drug therapy,

single agent is administered at higher dose and so there are higher chances of side effects. But in fix dose combination this issue can be overcome by lowering the dose of drugs in combination by doing this the risk of dose dependent side effects are resolved.

3. **Adherence** – In order to achieve long term reduction in blood pressure, the patient needs to adhere to the treatment and take pills three to four times a day. This results in a constant burden on the patient, especially in elderly age persons. Whereas cost of different pill also increases the financial burden on some patients. Thus fix dose combination therapy also help in decreasing dosage frequency well as reducing cost of the product.

Advantages of fix dose combination verses monodrug therapy

Table 1.2 Comparison of fix dose and monodrug therapy

FIX –DOSE COMBINATION	MONO DRUG THERAPY
Less cost	High cost
Convenience	Inconvenient
Compliance	Non-compliance
Less side effect	More side effect
More efficiency	More anti- hypertensive agent needed

Most widely used combination:-

1. Thiazide diuretic plus ACE inhibitors/ ARBs
2. Thiazide diuretic plus beta blockers
3. Thiazide diuretic plus calcium channel blockers
4. Beta blockers plus ACE inhibitors/ ARBs

Less effective combinations

1. ACE inhibitors plus ARBs
2. ARBs plus Beta – blockers
3. Beta-blockers plus centrally acting agents

1.3 INTRODUCTION TO ORAL DRUG DELIVERY SYSTEM(Ahir, Mali, Hajare, Bhagwat, & Patrekar, 2015; Manish Jaimini, Ranga, Kumar, Sharma, & Chauhan, 2013)

The most accepted route of drug administration is considered to be the oral route for the reason that of oral route of administration provides better patient compliance, lesser manufacturing cost when compared to other dosages forms and for its systemic effects.

As tablets is unit dosage form it provides very accurate dosing. Another reason for tablet is to most acceptable means of dosage administration is that they are self- administrated.

Tablets are a solid dosage form of medicaments with or without excipients which are prepared by compression method. According to the Indian Pharmacopoeia tablets are solid, flat or biconvex unit dosage form of a medicament alone or medicament along with excipients prepared by compressing technique.

Tablets are generally available in different shapes, sizes, weight and colures based on drug and its means of administration.

Tablets consist of 70 % of market for administration of drugs. Almost all drugs can be formulated in tablet dosage form except some drugs based on their physiochemical properties.

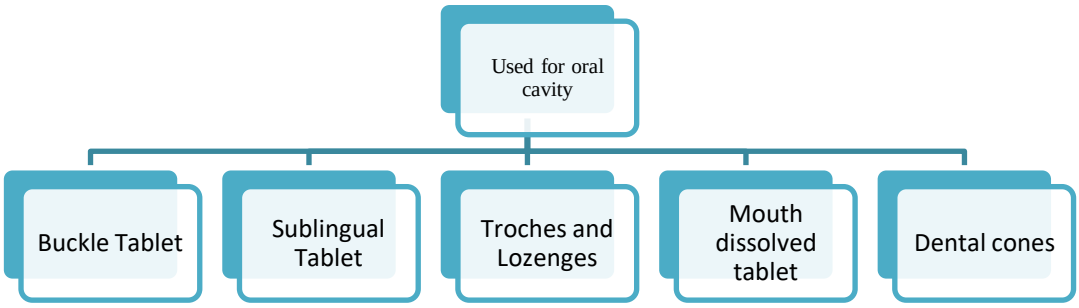
Tablet dosage form is most stable when compared to all oral dosage forms. Sterile conditions are required for manufacturing of parental and liquid dosage form but in solid oral delivery systems do not require sterile conditions and thus they reduce the cost of manufacturing.

Properties of an Ideal Tablet:

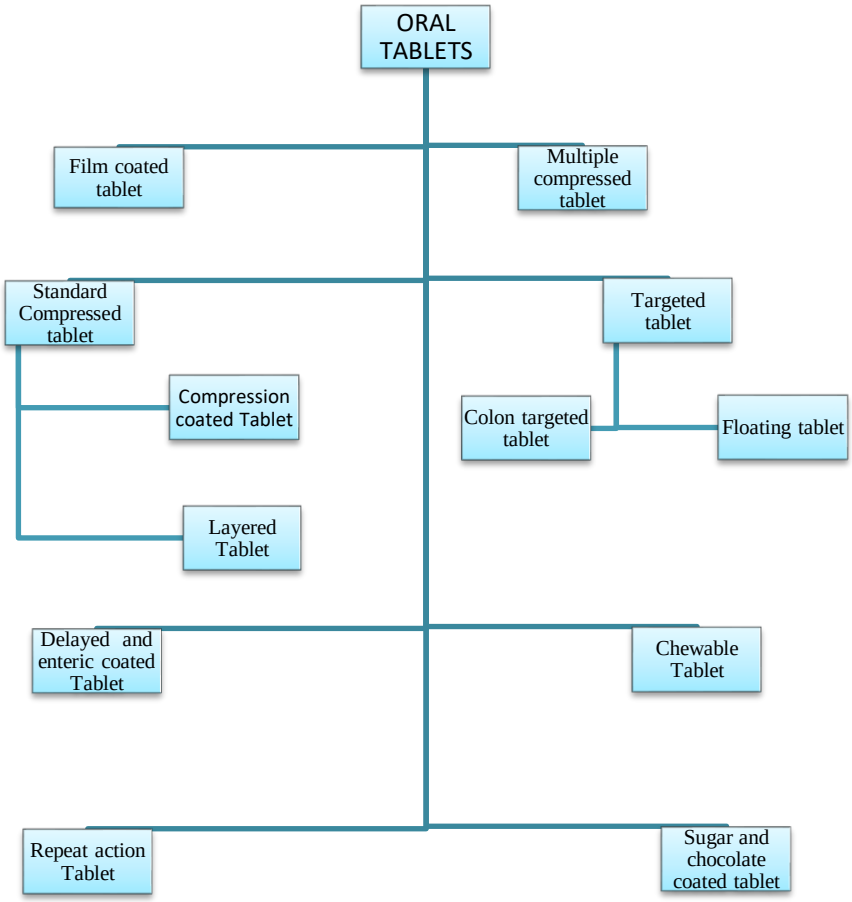
- Ideal Tablet should have good physical appearance without any defect.
- Should be physically and chemically stable.
- Should not cause any interaction.
- Should be able to release drug in pre determined rate.

Classification of Tablets:

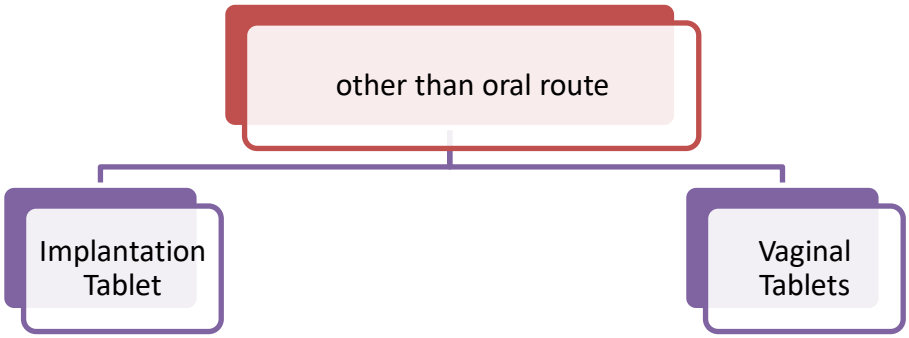
1. Used for oral cavity



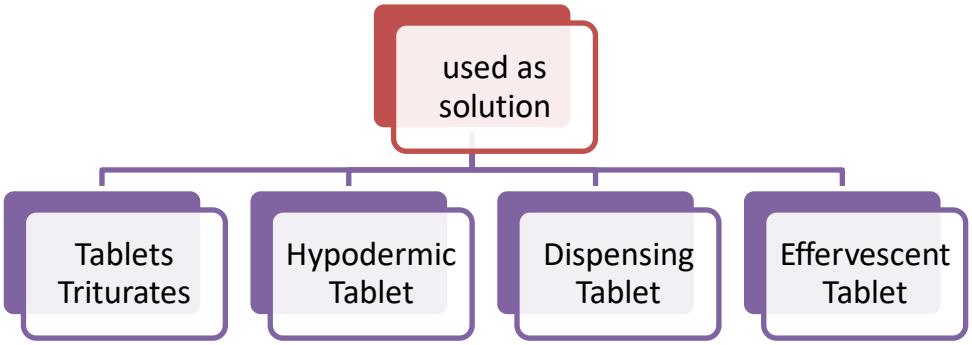
2. Based upon either route of administration or purpose,



3. Tablets administered by other routes:



4. Tablets used to prepare solution:



METHODS OF TABLET MANUFACTURING

Direct compression:

Direct compression method is most commonly used for crystalline substance which are possessing good physical properties.

Mostly direct compression is used for saving time and having cheaper cost of production.

Wet granulation:

Wet granulation techniques used for powered which is having poor flow property this method generally utilizes binding solution to prepare lump and then granulate and tablets are prepared.

Dry granulation:

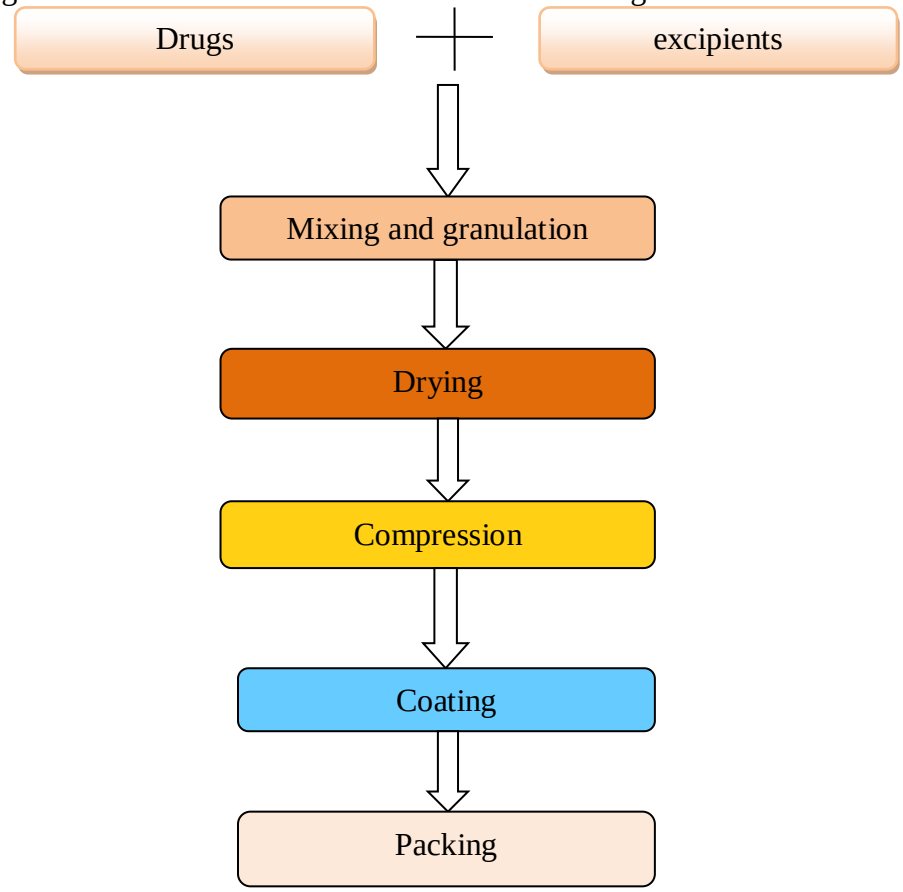
In process granules are prepared without using binder solution. The Substance which is sensitive to moister and heat is prepared using this procedure.

Slugs are known as the compacted mass and the process is called slugging. Screening and milling is then done with the slugs to obtain uniform power which increases the flow

property. The main benefits of using this processes is it reduces cost; time and equipment as well as it can be used for material prone to heat and moisture.

Unit operations involved in tablet manufacturing

Figure 1.3.1 Process involve in tablet manufacturing



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

1.4 INTRODUCTION TO IMMEIDATE RELEASE DOSAGE FORM(Rathod, Kadam, Jadhav, & Bharkad, 2014)(Neeraj, Abhishek, Abhilash, Rubia, & Rajni, 2014)

The term "immediate release" implies to the dosage in which the release of medicament is at fastest rate.

Thus, this term excludes "modified", "controlled", "sustained", "prolonged", "extended" or "delayed" release of drug.

For immediate release formulations least 70% (preferably 80%) of active ingredient within 3- 4 hours, if possible 2 hours, further if at all possible within 1.5 hours, or more preferred within 30 hours of administration.

Desired criteria for immediate drug delivery system:-

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

Advantages of Immediate Release Drug Delivery System:

- Improved stability
- Improved compliance/added convenience
- It can be prepared with minimum dose of drug
- There is no dose dumping problem.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- More flexibility for adjusting the dose.
- Adaptable and amenable to existing processing and packaging machinery

- Cost- effective
- Allows high drug loading.
- Suitable for controlled/sustained release actives

1.5 INTRODUCTION TO PELLETS AND PELLETIZATION TECHNEQUES(Yadav & Verma, 2016)(Gandhi & Baheti, 2013)

- Multiparticulate drug delivery system are nowadays getting an immersed popularity as compared to single unit drug delivery due the reasons that they having advantages of predictable gastric emptying, no risk of dose dumping, flexible release patterns and increased bioavailability.
- Pellets are considered as one of the best and most treading multi-particulate dosage forms and the process by which fine powered mixture of drug and exciepient are converted into pellet is known as Pelletization.
- Pellets are generally about 0.5 mm and 1.5 mm in size. Therapeutic advantage is not the only single reason offered by pellets, they also offers various advantages like less irritation of the gastro-intestinal tract and a lowered risk of side effects due to dose dumping, besides pharmaceutical benefits which includes, good flow characteristics, constricted particle size distribution, less friable.
- Hard gelatin capsule is one of the way in which pellets can be filled in and administered, however it can also be compressed into tablets.

Pellet formation and growth

Generally there are four steps involved in pellet formation

- Nucleation

  In nucleation, primary particles are drawn together to form three-phase air–water–solid nuclei.

- Coalescence

  The collision of well-formed nuclei to form larger size particles is known as coalescence.

- Layering

  Successive addition of material on already formed nuclei is layering.

- abrasion transfer

Transfer of material from one particle to another without any preference in either direction is abrasion transfer.

- size reduction

  Well-formed particles may undergo size reduction due to attrition breakage and shatter

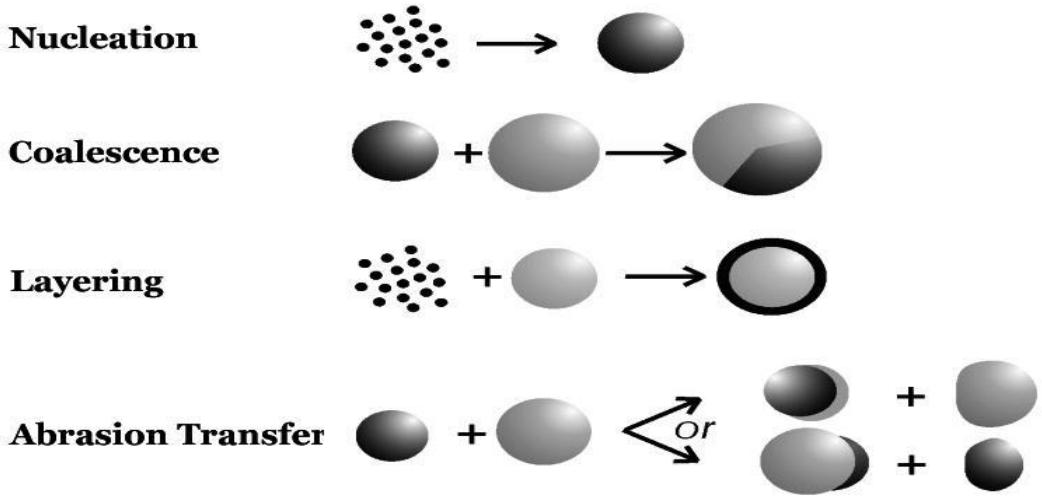


Figure 1.5.1 Process of pellet formation

Pelletization techniques

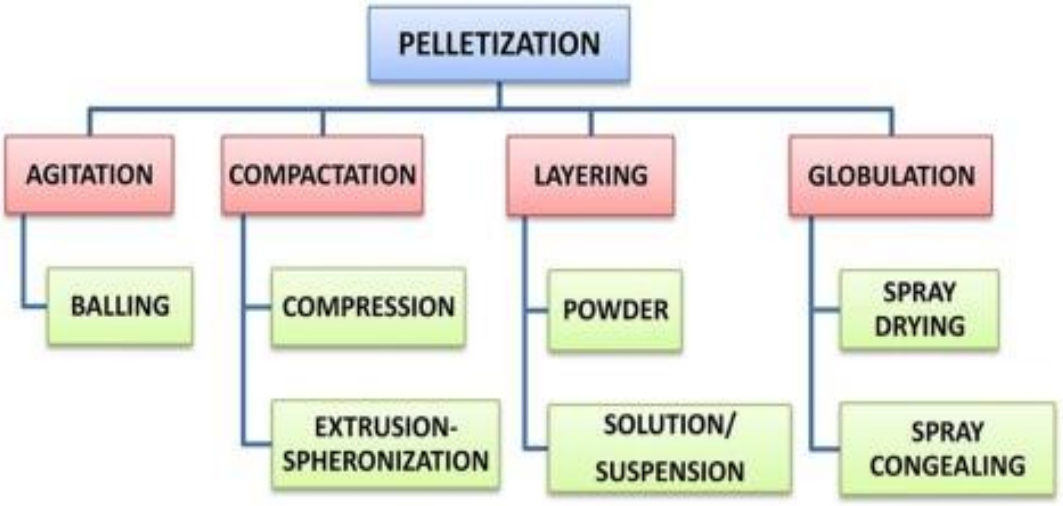


Figure 1.5.2 Pelletization technique

Excipients used in pellet formulation

- filler/diluent – to add bulk (dibasic calcium phosphate, lactose, microcrystallinecellulose,starch,sucrose)
- binders–to bind powders and maintain pellet integrity (hydroxypropylmethylcellulose, polyvinylpyrrolidone)
- lubricant–to reduce the coefficient of friction between individual particles or between the particles and the surfaces of the processing equipment(magnesiumstearate),
- separating agent – to promote the separation of pellets into distinct units during pelletization process(talc)
- disintegrant–to promote the disruption of pellets(croscarmellosesodium,sodiumstarch glycolate),
- spheronization enhancer – to facilitate the production of spherical pellets(microcrystallinecellulose)
- release modifier – to get the modified release from the pellet formulation (ethylcellulose, shellac)

Extrusion–spheronization

The extrusion–spheronization technique is the most popular method of producing pellets .

Process invoved

(i) preparation of the wet mass (granulation);

(ii) shaping the wet mass into cylinders (extrusion)

(iii) breaking up the extrudate and rounding of the particles into spheres (spheronization);

(iv) drying of the pellets

Steps and equipment used in extrusion–spheronization

1. Granulation

Granulation involves preparation of the plastic mass of the material. Different types of granulators are used to perform the mixing of the powder blend and the granulation liquid. The most commonly used granulators are a planetary mixer,highshear or sigma blade mixer The wet granulation process plays an important role in extrusion–spheronization.

2. Extrusion

Prepared plastic mass undergoes extrusion in which pressure is applied to a mass until it flows out through an orifice to produce the extrudates.The extrudate length may vary,depending on the physical characteristics of the materials to be extruded, method of extrusion, and how particles are main classes of extruders: screw,sieve and basket,roll,and ram extruder.

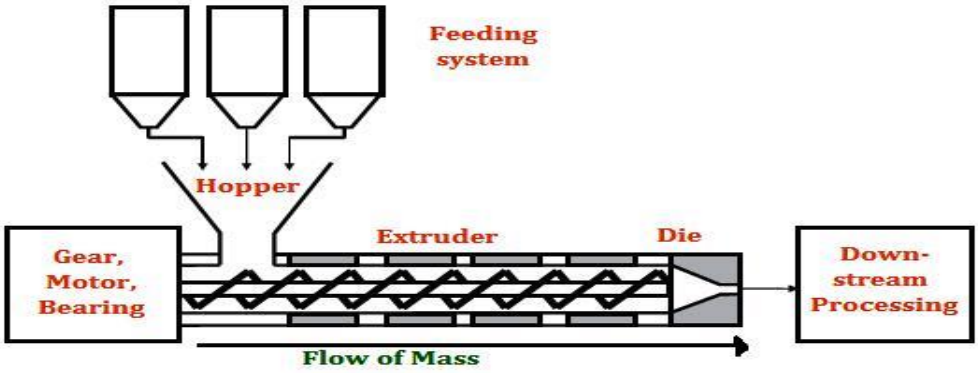


Figure 1.5.3 Diagram of extruder.

3. Spheronization

In spheronization, the extruded, cylindrically shaped particles are broken into uniform lengths and are gradually transformed into spherical shapes; this shaping process is due to plastic deformation. As extrudates are first broken into nearly uniform lengths, all three dimensions of agglomerate shape are determined, and spheres with a nearly uniform diameter are produced.

In the spheronization process,different stages can be distinguished depending on the shape of the particles,i.e.,starting from a cylinder over a cylinder with rounded edges,dumbbells,and elliptical particles to eventually perfect spheres In this mechanism, a twisting of the cylinder occurs after the formation of cylinders with rounded edges, finally resulting in the breaking of the cylinder into two distinct parts. Both parts have around and a flat side.

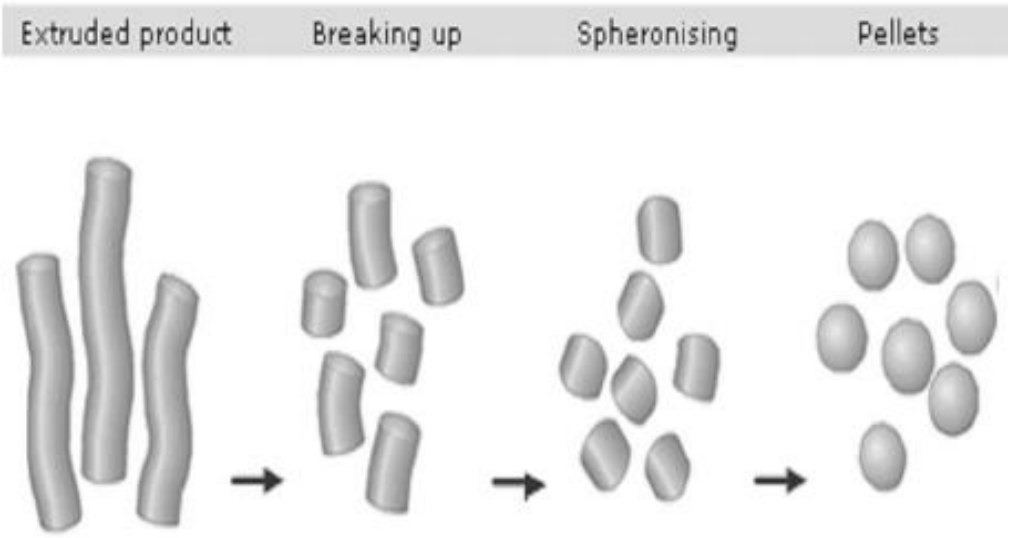


Figure 1.5.4 Process of spheronizer

Due to the rotational and the frictional forces involved in the spheronization process, the edges of the flat side fold together like a flower forming the cavity observed in certain pellets.

A spheronizer is a device consisting of a vertical hallow cylinder with a horizontal rotating disk(frictionplate) located inside Extrudates are charged onto the rotating plate and broken into short segments by contact with friction plate, collisions between particles and collisions with the wall. Mechanical energy introduced by the spinning friction plate is transmitted into kinetic energy in the form of mechanically fluidized bed.

Further processing will cause the extrudate to deform gradually into a spherical shape. The friction plate has a grooved surface to increase the frictional forces.

Two types of the geometry of the grooves exist,

1. cross-hatch geometry angles
2. Radial geometry

4. Drying

The fourth and final step of the process is the drying of the pellets .The pellets can be dried at room temperature or at elevated temperature in a fluidized bed or in an oven.

Parameters influencing final pellet quality

1. Formulation parameters
   1. Moisture content
   2. Granulating liquid
   3. Excipients
   4. Drugs Extrusion/spheronization technique
2. Equipment parameters
   1. Mixer
   2. Extruder
   3. Friction plate
   4. Extrusion screen
3. Process parameters
   1. Extrusion speed
   2. Extrusion temperature
   3. Spheronizer load
   4. Spheronization time
   5. Spheronization speed.
   6. Drying method.

1.6 INTRODUCTION TO DRUG

DRUG A

1.	Chemical Formula	$C_{20}H_{28}N_2O_5$
2.	Categories	ACE-inhibitor
3.	MOA	angiotensin I is converted to angiotensin II by an angiotensin-converting enzyme (ACE). Angiotensin II constricts blood vessels, increasing blood pressure. Enalaprilat, the active metabolite of enalapril, inhibits ACE. Inhibition of ACE decreases levels of angiotensin II leading to less vasoconstriction and decreased blood pressure
3.	Weight	376.4467gm/mol
4.	Absorption	55-75%, absorption is unaffected by food; poorly absorbed, 3-12%, due to its high polarity
5.	Protein binding	50-60% of prodrug is bound to plasma proteins
6.	Half life	< 2 hours for unchanged in health individuals, may be increased in those with congestive heart failure (3.4 and 5.8 hours for single 5- and 10-mg doses, respectively). The average terminal half life of enalaprilat is 35-38 hours. The effective half life following multiple doses is 11-14 hours.
7.	Melting point	266-268(°C)
8.	water solubility	722 mg/L (at 25 °C)
9.	pKa	7.9
10.	Route of elimination	Renal

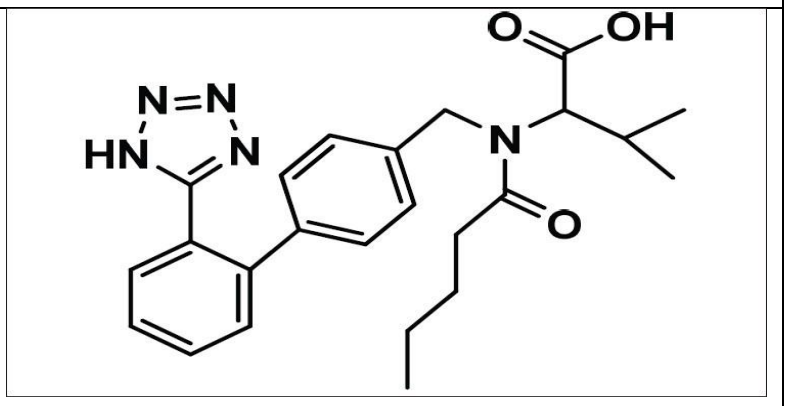
11.	Adverse effect	Blurred vision, confusion, dizziness, faintness, or light, headedness when getting up suddenly from a lying or sitting position, sweating unusual tiredness or weakness
12.	Dose	10 to 40 mg orally per day

DRUG B

1.	Chemical Formula	$C_7H_8ClN_3O_4S_2$
2.	Categories	Anti –hypertensive
3.	MOA	A thiazide diuretic often considered the prototypical member of this class. It reduces the reabsorption of electrolytes from the renal tubules. This results in increased excretion of water and electrolytes, including sodium, potassium, chloride, and magnesium. It has been used in the treatment of several disorders including edema, hypertension, diabetes insipidus, and hypoparathyroidism
3.	Weight	297.739 gm/mol
4.	Absorption	50-60%
5.	Protein binding	67.9%
6.	Half life	5.6 and 14.8 hours
7.	Melting point	266-268(°C)
8.	water solubility	722 mg/L (at 25 ℃)
9.	pKa	7.9
10.	Route of elimination	It is not metabolized but is eliminated rapidly by the kidney. It also crosses the placental but not the blood-brain barrier and is excreted in breast milk.
11.	Adverse effect	Seizures or convulsions, Decreased urine, Thirst, Muscle weakness, Constipation, Blurred

		vision, Dizziness, Photosensitivity, Drowsiness, Dry mouth/excessive thirst, Increased heart rate, Muscle pain, Nausea, Vomiting, Fatigue, Weakness
12.	Dose	The usual dose is 12.5 to 50 mg once daily.

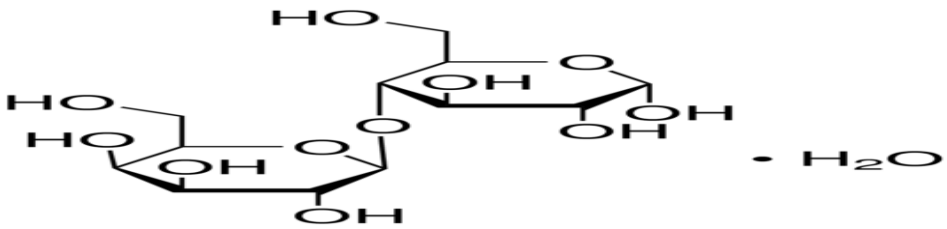
DRUG C

1.	Chemical Formula	$C_{24}H_{29}N_5O_3$
2.	Categories	Anti –hypertensive
3.	MOA	Valsartan 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. This effectively inhibits the AT1-mediated vasoconstrictive and aldosterone-secreting effects of angiotensin II and results in a decrease in vascular resistance and blood pressure. Valsartan is selective for AT1 and has virtually no affinity for AT2.
3.	Weight	435.528 g/mol
4.	Structure	
5.	Absorption	2-4 h after oral administration
6.	Protein binding	94 - 97%
7.	Half life	The initial phase $t_{1/2\ \alpha}$ is < 1 hour while the terminal phase $t_{1/2\ \beta}$ is 5-9 hours.
8.	Melting point	116-117 °C

9.	water solubility	In water, 1.406 mg/L at 25 deg C
10.	pKa	5.8
11.	Route of elimination	83% of absorbed drug is excreted in feces and 13% is excreted in urine, primarily as unchanged drug
12.	Adverse effect	headache, dizziness, fatigue, abdominal pain,cough, diarrhea and nausea.
13.	Dose	40, 80, 160 and 320 mg.

1.7 INTRODUCTION TO EXCEPIENTS("Handbook of Pharmaceutical Excipients – 7th Edition," 2013)

1. LACTOSE MONOHYDRATE

1.Nonproprietary Names
BP: Lactose monohydrate PhEur: Lactosum monohydricum JP:Lactose USPNF: Lactose monohydrate
2. Chemical Name
O-b-D-Galactopyranosyl-(1!4)-a-D-glucopyranose monohydrate
3.CAS Registry Number
[64044-51-5] 4
4.Empirical Formula
$C_{12}H_{22}O_{11}H_2O$
5.Molecular Weight
360.31 5gm/mol
6.Structural formula
 Figure 1.7.1 structure of lactose monohydrate
7.Functional Category
Binding agent Diluent for dry-powder inhalers Tablet binder Tablet and capsule diluent.
8.Method of Manufacture Lactose

Commercially, lactose is produced from the whey of cows' milk; whey being the residual liquid of the milk following cheese and casein production. Cows' milk contains 4.4–5.2% lactose; lactose constitutes 38% of the total solid content of milk. a-Lactose monohydrate is prepared by crystallization from supersaturated solutions below 93.58°C. Direct compression grades of a-lactose monohydrate are prepared by granulation/agglomeration and spray-drying.
9. Applications in Pharmaceutical Formulation
Various lactose grades are commercially available that have different physical properties such as particle size distribution and flow characteristics. This permits the selection of the most suitable material for a particular application; for example, the particle size range selected for capsules is often dependent on the type of encapsulating machine used. Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine size permits better mixing with other formulation ingredients and utilizes the binder more efficiently. Direct-compression grades are often used to carry lower quantities of drug and this permits tablets to be made without granulation.
10.Stability and Storage Conditions
Mold growth may occur under humid conditions. Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions. Lactose should be stored in a well-closed container in a cool, dry place.
11.Incompatibilities
A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products. Lactose is also incompatible with amino acids, aminophylline,amfetamines, and lisinopril
12.Safety

Adverse reactions to lactose are largely attributed to lactose intolerance, which occurs in individuals with a deficiency of the intestinal enzyme lactase.
13.Handling Precautions
Observe normal precautions appropriate to the circumstances and quantity of material handled. Excessive generation of dust, or inhalation of dust, should be avoided.

2. PREGELATINIZES STARCH

1.Nonproprietary Names
BP: Pregelatinised starch PhEur: Amylum pregelificatum USPNF: Pregelatinized starch
2.Synonyms
Compressible starch, Instastarch, Lycatab C, Lycatab PGS ,Merigel
3.Chemical Name
Pregelatinized starch
4.CAS Registry Number
[9005-25-8]
5.Empirical Formula
$(C_6H_{10}O_5)n$ where n = 300–1000
6.Structural Formula

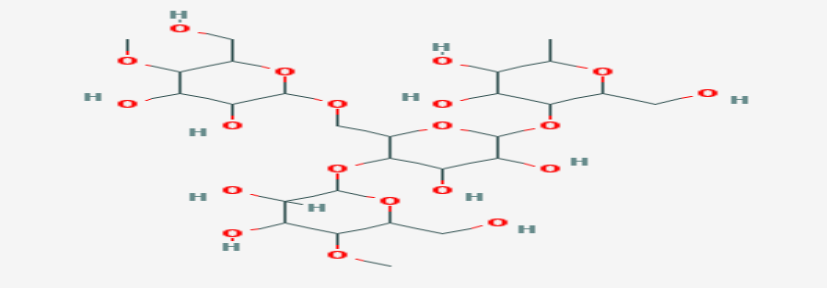



Figure1.7.2 Structure of pregelatinized starch
7.Functional Category

Tablet and capsule diluents

Tablet and capsule disintegrant

Tablet binder.

8.Applications in Pharmaceutical Formulation

Pregelatinized starch is a modified starch used in oral capsule and tablet formulations as a binder, diluent, and disintegrant.

Incomparison to starch, grades of pregelatinized starch may be produced with enhanced flow and compression characteristics such that the pregelatinized material may be used as a tablet binder in dry-compression or direct compression processes. In such processes, pregelatinized starch is self lubricating. However, when it is used with other excipients it may be necessary to addalubricant toa formulation. Although magnesium stearate 0.25% w/w is commonly used for this purpose, concentrations greater than this may have adverse effects on tablet strength and dissolution. Therefore, stearic acid is generally the preferred lubricant with pregelatinized starch.

8.Description

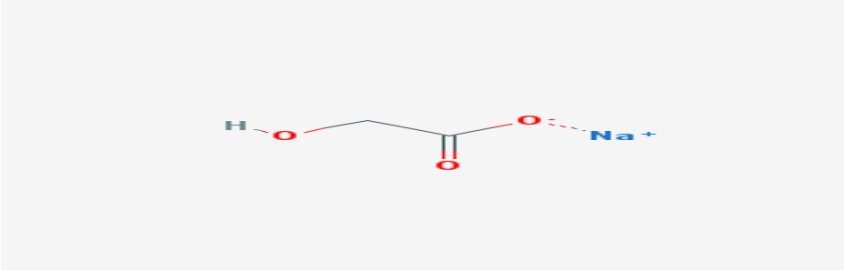
Pregelatinized starch occurs as a moderately coarse to fine, white to off- white colored powder. It is odorless and has a slight characteristic taste. Examination of fully pregelatinized starch as slurry in cold water, under a polarizing microscope, reveals no significant ungelatinized granules.

9.Typical properties

1	Acidity/ alkalinity:	pH = 4.5–7.0 for a 10% w/v aqueous dispersion
2	Angle of repose:	40.78
3	Density (bulk):	0.586g/cm3
4	Density (tapped):	0.879g/cm3
5	Density (true):	1.516g/cm3
6	Flowability:	18–23%
7	Moisture content:	Pregelatinized maize starch is hygroscopic.
8	Particle size	30–150mm

9	Solubility:	Practically insoluble in organic solvents. Slightly soluble to soluble in cold water, depending upon the degree of pregelatinization. Pastes can be prepared by sifting the pregelatinized starch into stirred, cold water. Cold-water soluble matter for partially pregelatinized starch is10–20%.
10.Stability and Storage Conditions		
Pregelatinized starch is stable but hygroscopic material, which should be stored in a well-closed container in a cool, dry place.		
11.Method of Manufacture		
Pregelatinized starches are prepared by heating an aqueous slurry containing up to 42% w/w of starch at 62–728C. Chemical additives that may be included in the slurry are gelatinization aids (salts or bases) and surfactants, added to control rehydration or minimize stickiness during drying. After heating, the slurry may be spray-dried, roll-dried, extruded, or drum-dried. In the last case, the dried material may be processed to produce a desired particle size range. Pharmaceutical grades of fully pregelatinized starch use no additives and are prepared by spreading an aqueous suspension of ungelatinized starch on hot drums where gelatinization and subsequent drying takes place.		
12.Safety		
Pregelatinized starch and starch are widely used in oral solid dosage formulations. Pregelatinized starch is generally regarded as a nontoxic and nonirritant excipient. However, oral consumption of large amounts of pregelatinized starch may be harmful.		
13.Regulatory Status		
Included in the FDA Inactive Ingredients Guide (oral capsules, suspensions, and tablets; vaginal preparations). Included in non parenteral medicines licensed in the UK.		
14. Related Substances		
Starch; starch, sterilizable maize		

3. SODIUM STEARYL FUMARATE

1.Nonproprietary Name
BP: Sodium stearyl fumarate PhEur: Natrii stearylis fumaras USPNF: Sodium stearyl fumarate
2.Synonyms Fumaric acid, octadecyl ester, sodium salt; Pruv; sodium monostearyl fumarate.
3.Chemical Name
2-Butenedioic acid, monooctadecyl ester, sodium salt
4.CAS Registry Number
[407080-8]
5.Empirical Formula
$C_{22}H_{39}NaO_4$
6.Molecular Weight 390.5gm/mol
7.Structural Formula  Figure 1.7.3 structure of sodium stearly fumarate
9.Functional Category Tablet and capsule lubricant.
10.Applications in Pharmaceutical Formulation
Sodium stearyl fumarate is used as a lubricant in capsule and tablet formulations at 0.5–2.0% w/w concentration.It is also used in certain food applications. **11. Description**
Sodium stearyl fumarate is a fine, white powder with agglomerates of flat,

circular-shaped particles.		
10.Typical properties		
1	Acidity/alkalinity:	pH = 8.3 for a 5% w/v aqueous solution at 908C.
2	Density:	1.107g/cm3
3	Density (bulk):	0.2–0.35g/cm3
4	Density (tapped):	0.3–0.5g/cm3
5	Melting point:	224–2458 ^{0}C (with decomposition)
6	Solubility	Water 1 in 20000 at 258 ^{0}C 1 in 10 at 80 8 ^{0}C
11.Stability and Storage Conditions		
At ambient temperature, sodium stearyl fumarate is stable for up to 3 years when stored in amber glass bottles with polyethylene screw caps. The bulk material should be stored in a well-closed container in a cool, dry place.		
12.Incompatibilities		
Sodium stearyl fumarate is reported to be incompatible with chlorhexidine acetate.		
13.Method of Manufacture		
Stearyl alcohol is reacted with maleic anhydride. The product of this reaction then undergoes an isomerization step followed by salt formation to produce sodium stearyl fumarate.		
14.Safety		
Sodium stearyl fumarate is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material.		
15.Handling Precautions		
Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium stearyl fumarate should be handled in a well-ventilated environment; eye protection is recommended.		
16.Regulatory Status		

Permitted by the FDA for direct addition to food for human up to 0.2–1.0% by weight of the food. Included in non parenteral medicines licensed in the UK. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

4. MAGNESIUM STERATE

1.Nonproprietary Names
BP: Magnesium stearate JP: Magnesium stearate PhEur: Magnesii stearas USPNF: Magnesium stearate
2 .Synonyms
Magnesiumoctadecanoate; octadecanoic acid,magnesium salt; stearic acid, magnesium salt.
3.Chemical Name
Octadecanoic acid magnesium salt
4.CAS Registry Number
[557-04-0]
5.Empirical Formula
$C_{36}H_{70}MgO_4$
6.Molecular Weight
591.34 gm/mol
7.Structural Formula
$[CH_3(CH_2)_{16}COO]_2Mg$
8.Functional Category Tablet and capsule lubricant
9.Applications in Pharmaceutical Formulation
Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in

barrier creams.

10.Description

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

11.Typical properties

1	Crystalline forms	high-purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate
2	Density (bulk):	0.159g/cm3
3	Density (tapped):	0.286g/cm3
4	Density (true):	1.092g/cm3
5	Flowability	Poorly flowing, cohesive powder.
6	Melting range:	117–1508^{0}C (commercial samples); 126–1308^{0}C (high purity magnesium stearate).
7	Solubility	practicallyinsolubleinethanol,ethanol(95%),ether and water; slightly soluble in warm benzene and warm ethanol (95%)
8	Specific surface area	1.6–14.8m^2/g

12. Stability and Storage Conditions.

Magnesium stearate is stable and should be stored in a wellclosed container in a cool, dry place

13.Incompatibilities

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

14.Method of Manufacture
Magnesium stearate is prepared either by the interaction of aqueous solutions of magnesium chloride with sodium stearate or by the interaction of magnesium oxide, hydroxide, or carbonate with stearic acid at elevated temperatures.
15.Safety Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation.
16. Handling Precautions.
Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing, and choking. Magnesium stearate should be handled in a well ventilated environment; a respirator is recommended

5. IRON OXIDE YELLOW

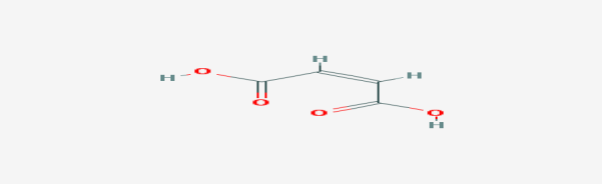
1 Nonproprietary Names
None adopted.
2 Synonyms
Iron oxide yellow monohydrate: E172 Hydrated ferric oxide Iron (III) oxide monohydrate Yellow Mapico yellow Pigment yellow 42 Yellow ferric oxide.
3 Chemical Name
Iron oxide yellow monohydrate

4.CAS Registry Number
[51274-00-1]
5 Empirical Formula
$Fe_2O_3H_2O$
6 Molecular Weight
177.70 g/mol
7. Structural Formula
Iron oxides are defined as inorganic compounds consisting of any one of or combinations of synthetically prepared iron oxides, including the hydrated forms
8. Functional Category
Colorants.
9. Applications in Pharmaceutical Formulation
Iron oxides are widely used in cosmetics, foods, and pharmaceutical applications as colorants and UV absorbers. As inorganic colorants they are becoming of increasing importance as a result of the limitations affecting some synthetic organic dyestuffs. However, iron oxides also have restrictions in some countries on the quantities that may be consumed and technically their use is restricted because of their limited color range and their abrasiveness.
10. Description
Iron oxides occur as yellow, red, black, or brown powder. The color depends on the particle size and shape, and the amount of combined water.
11 Stability and Storage Conditions
Iron oxides should be stored in well-closed containers stored in a cool, dry, place.
12 Incompatibilities
Iron oxides have been reported to make hard gelatin capsules brittle at higher temperatures when the residual moisture is 11–12%. This factor affects the use of iron oxides for coloring hard gelatin capsules, and will limit the amount that can be incorporated into the gelatin material.

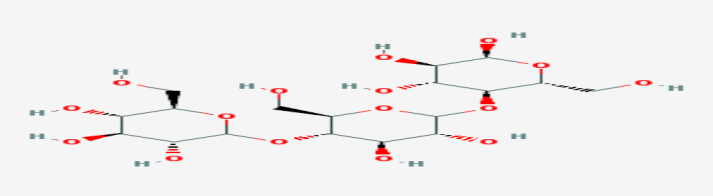
13 Safety
Iron oxides are widely used in cosmetics, foods, and oral and topical pharmaceutical applications. They are generally regarded as nontoxic and nonirritant excipients. The use of iron oxide colorants is limited in some countries, such as the USA, to a maximum ingestion of 5mg of elemental iron per day.
14 Handling Precautions
Observe normal precautions appropriate to the circumstances and quantity of the material handled. In the UK, the occupational exposure limits for iron oxide fumes (as Fe) are 5mg/m^3 long-term (8-hour TWA) and 10mg/m^3 short-term.
15 Regulatory Status
Accepted for use as a food additive in Europe. Included in nonparenteral medicines licensed in many countries including Japan, UK, and USA.

6. MELEIC ACID

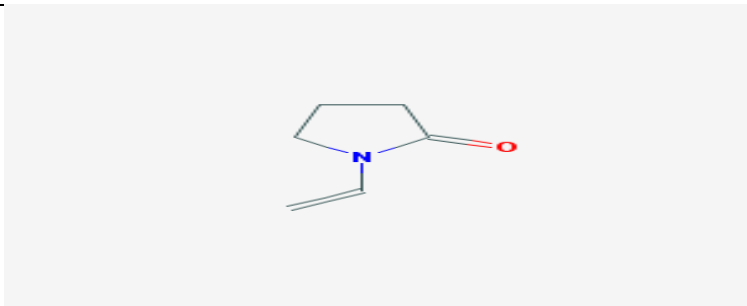
1 Nonproprietary Names
maleic acid, ammonium salt maleic acid, dipotassium salt maleic acid, disodium salt maleic acid, iron salt
2 Synonyms
hydrogen maleate maleate
3 Chemical Name
Maleic acid; Cis-butenedioic acid; Toxilic acid
4.CAS Registry Number
26099-09-2
5 Empirical Formula
$C_4H_4O_4$ or HOOCCH=CHCOOH
6 Molecular Weight

116.072 g/mol
7. Structural Formula
 Figure 1.7.4 structure of Meleic acid
8. Functional Category
Stabilizer
9. Applications in Pharmaceutical Formulation
Maleic acid may be used to form acid addition salts with drugs to make them more stable
10. Description
Maleic acid is a colorless crystalline solid having a faint odor. It is combustible though it may take some effort to ignite. It is soluble in water.
11 Stability and Storage Conditions
Storage away from direct light.
12 Incompatibilities
Strong bases and Strong acids
13 Safety
The substance irritates severely the eyes, the skin and the respiratory tract on short term exposure
14 Handling Precautions
Avoid all personal contact, including inhalation
15 Regulatory Status
Approved in US FDA and in Europe and Canada.

7. MICROCRYSTALLINE CELLULOSE

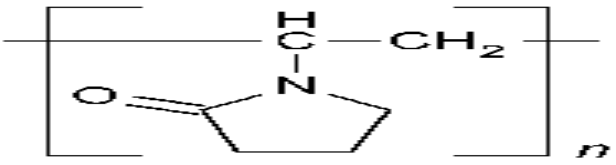
1.Nonproprietary Names
Cellulose gel
2. Chemical Name
Cellulose
3.CAS Registry Number
9004-34-6
4.Empirical Formula
$(C_6H_{10}O_5)n$
5.Molecular Weight
504.438 g/mol
6.Structural formula
 Figure 1.7.5 Structure of Microcrystalline cellulose
7.Functional Category
Emulsifier, stabilizer, anticaking agent, dispersing agent
8.Description
Fine, white or almost white, odourless, free flowing crystalline powder.
9. Applications in Pharmaceutical Formulation
Microcrystalline cellulose is a commonly used excipient in the pharmaceutical industry. It has excellent compressibility properties and is used in solid dose forms, such as tablets. Tablets can be formed that are hard, but dissolve quickly.
10. Stability and Storage Conditions
Preserve in tight containers

8. POLYVINYLPYROLIDONE

1.Nonproprietary Names
Povidone, Povidonum, PVP
2. Chemical Name
1-vinyl-2-pyrrolidone N- vinyl pyrrolidone N-vinyl-2-pyrrolidinone N-vinylpyrrolidone
3.CAS Registry Number
9003-39-8
4.Empirical Formula
$(C_6H_9NO)n$
5.Molecular Weight
111.144 g/mol
6.Structural formula
 Figure 1.7.6 Structure of Polyvinylpyrolidone
7.Functional Category
Binder
8.Description
MCC is purified, partially depolymerized cellulose that occurs as a white, odourless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades, which have different properties and applications.
9. Applications in Pharmaceutical Formulation

Binder for tablets and capsules, a film former for ophthalmic solutions, to aid in flavoring liquids and chewable tablets, and as an adhesive for transdermal systems.
10. Safety & Incompatibilities
PVP is physiologically inert. It is stable and compatible with most of drug and exciepient at normal room temperature.

9. CROSSPOVIDONE

1.Nonproprietary Names
Crospovidone ,Crospolividone ,Polyvidon, Polyvidon, Polyvinylpolypyrrolidone
2. Chemical Name
1-Vinyl-2-pyrrolidinone polymer, croβlinked Croβ-linked homopolymer of 1-Etenylpyrrolidin-2-one
3.CAS Registry Number
0009003-39-8
4.Empirical Formula
$(C_6\text{-}H_9\text{-}N\text{-}O)n$
5.Molecular Weight
111.143 g/mol
6.Structural formula
 Figure 1.7.7 Structure of Crosspovidone
7.Functional Category
Tablet disintegrant
8. Description
It is a white to creamy white, finely divided, free-flowing, practically tasteless,

odorless or nearly odorless, hygroscopic powder.
9. Applications in Pharmaceutical Formulation
Water insoluble tablet disintegrant used at 2-5% concentration in tablets prepared by direct compression or wet and dry granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity with little tendency to form gels.
10.Stability and Storage Conditions
Crospovidone is stable. However, since it is hygroscopic it should be stored in an airtight container in a cool, dry place.
11.Incompatibilities
Compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level CP may form molecular adducts with some materials

CHAPTER 2

AIM AND OBJECTIVE

RATIONALE

- Mono-drug therapy for treatment of hypertension is not able to able to give the desired therapeutic result ,the the patient needs to be given multi –drug therapy
- But multi-drug therapy increases the number of pills to be administered every day. So in order to overcome this problem fix dose combination therapy can be used.
- Various product of fix dose combination are available in market for treatment of hypertension.
- Aim of this study was to develop, optimize and evaluate immediate release pellets of Drug A (20 mg) and Drug B (12.5 mg).
- To achieve the dissolution profile of optimized formulation with the innovator's product with specific time point and % drug release.
- Aim of this study was to develop, optimize and evaluate immediate release pellets of Drug C (80 mg) and Drug B (12.5 mg).
- To compare the dissolution profile with the innovator's product.

Objective

- To formulate the IR tablets containing fix dose combination of anti-hypertensive agents.
- To study the effect of composition of various excipients on tablet characteristic.
- To compare or match the in-vitro release and tablet characteristic of the designed developed formulation with the innovator formulation.
- To formulate the IR pellets containing fix dose combination of anti-hypertensive agents.
- To optimize Formulation parameter like effect of solvent and effect of disintegrating agent and to optimize Process parameter like speed of spheronizer
- To compare or match the in-vitro release and pellets characteristic of the designed developed formulation with the innovator formulation.
- To compare the IR tablet dosage form v/s multiparticulated drug delivery pellets.

CHAPTER 3

LITERATURE REVIEW

1.Immediate release dosage form					
Sr. no	Title	Author	Year	Publication	Inference
1.	An Overview on Emerging Trends in Immediate Release Tablet Technologi-es	Pande V, et al.	2016	Austin Therapeutics - Volume 3 Issue	Delayed release of medicament leads to reduce the effectiveness of the treatment. Thus in order to overcome this issue immediate release has come into existence. To accomplish these therapeutic necessities, formulation and development scientist have dedicated substantial endeavor in development of novel type of tablet dosage forms. Developed of Immediate-Release Tablets for oral administration, one that disintegrates

					and dissolves rapidly with improve dissolution and also for selection of Excipients can be a better way of overcoming such issues.
2.	A review on immediate release tablet dosage form	Jishan Ali Ahmed et al	2015	Ijppr Vol. 2 (3): 1-17	Compared to all other route of administration oral route of delivery system is mostly used due to easy administration, no pain to patient, versatility and self administration Currently immediate release formulation are getting more attention and acceptance because of patient compliance are effectiveness. Market exclusivity is also increased

					for manufacturer for immediate release formulation.
3.	A Review in immediate Release Drug Delivery Systems	Mohalkar Rahul et. al.	2015	PHARMATUTOR	From few decades Conventional dosage forms were used for the treatment. Tablets are most commonly and widely used form of drug delivery. The fundamental approach for Immediate release solid dosages form development is by the use of using super-disintegrates which gives instant disintegration after administration. Wet granulation, direct compression are some techniques useful for development of such formulation. The immediate

					release dosage form are designed for immediate release of for rapid absorption.
4	Formulation and evaluation of immediate release tablets	Shafi Shaik, et. Al.	2014	IJRPB	The present study aims at developing a Drug immediate release tablet formulation for the effective treatment of congestive heart failure (CHF), as an adjunct to conventional treatments (ACE inhibitors and diuretics. To provide the patient with the most convenient mode of administration, there was need to develop immediate release dosage form, particularly one that disintegrates rapidly and

					disperse and help in enhancing the bioavailability .
5	Immediate release drug delivery system (tablets): overview	Rishikesh et al.	2013	International Research Journal of Pharmaceutical and Applied Sciences (IRJPAS)	The immediate release tablets give the benefit of precise dosing in combination with releasing of the drug at a faster rate. Because of the technology available today the formation, handling and storage cost is such formulation is equivalent to conventional tablets.
6	A Review on Immediate Release Drug Delivery System	Manish Jaimini and Saurabh Rawat	2012	Research Journal of Pharmaceutical, Biological and Chemical Sciences	Oral route of drug administration is considered as one of the most safe, convenient and cost effective route of drug administration. The main disadvantage of

					this route of drug administration is that it is not preferable which quick onset of action is required but it can be now achieved by immediate release drug delivery system just by addition of disintegration agent.
Pelletization					
1	Pharmaceutical Pellets: A Versatile Carrier for Oral Controlled Delivery of Drugs	Niti Yadav and Anurag Verma	2016	Asian Journal of Pharmaceutical Education and Research	Pellets are multiparticulate dosage forms which are agglomeration of fine powder excipient and drugs which cause the development of small free flowing spherical particles by the technique called as pelletization process.This pellets

					are of varied between 500-1500 µm in size. Uniformity of dose, less dose dumping, less friability etc. is one of the main advantages with pellets.This layering, extrusion spheronization, cryopelletization, is the main technique involved in pellatiztion process.
2	Extrusion–spheronization a promising pelletization technique: In-depth review	Sagar Muley et. al.	2015	Asian journal of pharmaceutical sciences	This review article deals with various aspects of the extrusion–spheronization technique. The first part includes different steps in the production process of pellets such as granulation, extrusion, spheronization, and

					drying. In the second part, the parameters which can influence the quality of pellets including formulation (moisture content, granulating liquid, excipients, and drugs), equipment (mixer, extruder, friction plate, and extrusion screen) and process (extrusion speed, extrusion temperature, spheronizer load, spheronization time, spheronization speed, and drying method) are discussed. In the final part, methods available for characterization (particle size distribution,

					surface area, shape and sphericity, porosity, density, hardness and friability, flow properties, disintegration, and dissolution) of the pellets are explained
3.	Pellets and pellatization technique as multiparticulated drug delivery system as a conventional and novel approach	Srinivas R. et. al.	2015	International Journal of Institutional Pharmacy and Life Sciences	Pharmaceutical research and development are increasingly focusing on delivery systems which Enhance desirable therapeutic objectives while minimising side effects. Multiparticulate drug delivery systems are oral dosage forms consisting of multiplicity of small descrete units, in which

					active substance is present as a number of independent subunits. Multiparticulate drug delivery systems (MPDDS) are suitable for conventional as well as novel drug delivery techniques. Pelletization is a novel drug delivery system which converts the fine powder into pellets. The present work mainly focuses on the all aspects that are related to the formulation, evaluation and development of new techniques for pellts and pelletizaton which is usefull in site-specific drug

					delivery system. This work also projects novel techniques for pelletization such as cryopelletization, freezepelletization, Hmot melt extrusion and melt spheronization along with traditional techniques
Hypertension					
1	Fixed-Dose Combination Therapy—Is It Time for This Approach to Hypertension and Dyslipidemia Management.	Domenic A. Sica	2004	The journal of clinical hypertension	The case for fixed-dose combination antihypertensive and dyslipidemic therapy can be argued most vigorously in the context of the current control rate, which is approximately 10% for both disturbances jointly treated. Decreasing the total number of

					daily doses needed for joint BP and lipid control represents a major advantage of fixed-dose combinations. Thus, the use of once daily fixed-dose antihypertensive/dyslipidemic combinations can be expected to enhance medication compliance. However, if the antihypertensive component of this fixed-dose combination must be given twice daily, such supplemental dosing may reduce the previous gain in compliance.
2	The Role of Combination Therapy in the	Marvin Moser and	1998	American Journal of Hypertension	Only about half of the total population affected by

	Treatment of Hypertension	Henry R. Black			hypertension is cured by mono drug therapy. Therefore the increased utilization of fixed-dose combination treatment may make it more patient complaince This will also increase the rates of blood pressure control and ultimately decrease hypertension.

CHAPTER 4

EXPERIMENTAL WORK

4.1 LIST OF EQUIPMENT USED

Sr.No	Name of Equipment	Model	Supplier
1.	FETTE Compression Machine	102i	FETTE Compaction co
2.	27 station compression machine	CMB4 D27	Cadmach, Ahmedabad
3.	10 station compression machine	KMTC-10/BTOLL	Kambard, Mumbai
4	8 station compression machine	JMB-8	GMC, Ahmedabad
5	Rapid mixing granulator	RMG 1,3,5,10 L.	SARAL ENGG company
6	Fluidized bed dryer	TG-200	Retch Ltd
7	Fluidized bed drier	Pg119	PAM GLATT, Germany
8	Bulk Density apparatus	Etd1020	Electrolab, Mumbai
9	Octagonal blender	SS316GMP	Gansons, Mumbai
10	Oscillator granulator.	HD-410 ACWGS	Rimek Karnavati Engg
11	Dehumidifier	TNV2000	Tropical/ Nortec, Mumbai
12	Disintegration apparatus	Ed2al	Electro lab, Mumbai
13	Friability test apparatus	Ef/1w	Electro lab, Mumbai
14	IR balance	LJ16	Mettler Toledo, Japan
15	Multimill	MM-LAB-GMP	General machinery co. (GMC)
16	Conical mill	GMP LAB	Crystal Atomation
17	Planetary mixer	PLM-5 and GMP	Gansons Ltd

18	Schleuniger hardness	tester 6d	Dr. Schleuniger pharmatron, Mumbai
19	Vernier digital Caliper	Cd102	Mitutoyo corporation, Japan
20	Sieve shaker	RP 09	CISA, Barcelona
21	Stability chamber 25°C/60%RH	Nec2280rs	Neutronic,Mumbai
22	Stability chamber 30°C/65%RH	Nec-212rlos	Neutronic,Mumbai
23	Stability chamber 40°C/75% RH	Nec 212rlos	Neutronic, Mumbai
24	Tray drier	0865	Larsan & Toubro Ltd., Mumbai
25	Laboratory oven	NEC-416 PAC	Neutronic, Mumbai
26	Vibratory Sifter	So4 12	Sam techno mach., Ahmedabad
27	Weighting balance	AB204-S	Mettler Toledo, Japan
28	Weighting balance	BSA224 S-CW	Sartorius co. Ltd
29	UV Spectrophotometer	UV 1800	Shimadzu
28	Extruder	Cronimach	Cronimach machinery,Ahemdabad
29	Spheronizer	Cronimach	Cronimach machinery,Ahemdabad

4.2 LIST OF MATERIALS USED

SR.NO	CHEMICAL AND REAGENT	MANUFACTURED BY
1	Drug A	Dr. Reddy's Laboratories
2	Drug B	Icpa Laboratories and Torrent research centre gift sample
3	Drug C	Alembic gift sample
4	Microcrystalline cellulose	TCS gift sample
5	Crosspovidone	Yellow chem
6	Polyvinly pyrolidone	Yellow chem
7	Lactose Monohydrate	DFE Pharm
8	Pregelatinized starch	JRS Pharma
9	Maleic Acid	Wacker Chemie AG
10	Iron oxide yellow	Colourcon
11	Dried maize stach	Icpa Laboratories
12	Sodium steary fumarate (Rank)	Dr. Reddy's Laboratories
13	Sodium steary fumarate (Taiwan)	Ziuguin chemical
14	Magnesium stearate	Nikhita Pharma

4.3 PREFORMULATION STUDIES

Preformulation studies are initial study conducted in research and development process in which physico-chemical properties of a new drug substance are determined for development a dosage form which is safe effective and stable in human.

Hence, Preformulation studies on the obtained sample of drug for identification and compatibility studies were performed.

4.3.1 Characterization of the Drug:

4.3.1.1 Organoleptic properties:

The sample of Drug A, Drug B, Drug C was studied for organoleptic properties such as color, odor and Appearance.

4.3.1.2 Determination of solubility:

Solubility of the drugs was determined in 6 different media along the pH range of 1 to 7.5 pH.

Media selected for the study were water, methanol,0.1 N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer & pH 7.5 phosphate buffer.

The drugs were taken in excess quantity and solublized using mechanical shaker for 24 hours.

Then these drug suspensions were filtered and their absorbances were measured at the respective wavelengths of drugs using UV visible spectroscopy.

4.3.1.3 Melting point:

Melting point of all the drugs were determined using melting point apparatus. Finely dried powder of drug was inserted in dried capillary sealed from one side and the temperature at which drug started melting was measured. This range was compared with the reported value.

4.3.1.4 UV spectroscopy study:

Stock solution (100 µg/ml) of Drug A, Drug B, Drug C were prepared using methanol as a media and dilution was done to get 10 µg/ml standard solutions. These solutions were scanned in the range 200-400 nm to obtain λ max. The wavelength having maximum absorption was recorded for each sample.

4.3.1.5Calibration curves of Drug A and Drug B in methanol:

Accurately weighed quantities of Drug A, Drug B Drug C were dissolved in little quantity of methanol and volume was made up to 100 ml with water. Appropriate aliquots were taken into different volumetric flasks and made up to 10 ml with methanol, so as to get drug concentrations of 5 to 25 µg/ml.

4.3.1.6 Fourier transforms infrared spectroscopy (FTIR) study:

The samples (1 mg) were powdered and mixed with the (10 mg) of dry powdered potassium bromide. The powdered mixture was taken in a sampler and the spectrum was recorded by scanning in the wavelength region of 4000-400 cm^{-1} using FTIR spectrophotometer.

4.3.1.7 Differential scanning Calorimeter (DSC) study:

Solid dispersion of Drugs prepared by solvent evaporation method and they were found stable during preparation. No discoloration was found during heating or storage condition.

4.3.1.8 X- Ray Diffraction:

X-ray diffraction (XRD) pattern was recorded on a X-ray diffractometer with a CuKα radiations source, voltage 40KV, current 30mA, and a scanning rate of 2 degree/min.

4.3.1.9 Particle size analysis

Particle size analysis was carried out using Malvern Mastersizer equipped with 2000 Hydro MU (range 0.02µm-2000µm).

The particle size distribution analysis was carried out using a laser diffraction principle. All measurements were reported as average of triplicate readings.

4.3.2 Solid State Compatibility Studies of Drug with Excipients:

The drug-excipients interaction study was carried out by using physical observation of X- Ray Diffraction.

4.3.2.1Physical observations:

In this method, a small mixture of drug with excipients with the percentage of mixture and without any mixture is placed in a vial with rubber closure, in order to do hermetically seal. A storage period of two weeks at 400C, 75% RH in

Environmental Test Chamber is employed after which time period; the sample is to be observed.

4.4 FORMULATION AND EVALUATION OF IR TABLETS

The method used for formulation of immediate release tablets was ***wet granulation.***

4.4.1 List of ingredient used for final formulation

SR.NO	INGREDIENT	FUNCTION
1	Drug A	Anti-hypertensive agent
2	Drug B	Anti-hypertensive agent
3	Lactose monohydrate	Tablet diluent
4	Pregelatinized starch	Tablet binder
5	Maleic Acid	Stabilizer
6	Iron oxide yellow	Colorant
7	Dried maize stach	Disintegrate
8	Sodium steary fumarate (Rank)	Lubricant
9	Sodium steary fumarate (Taiwan)	Lubricant
10	Magnesium stearate	Lubricant

4.4.2 Manufacturing process

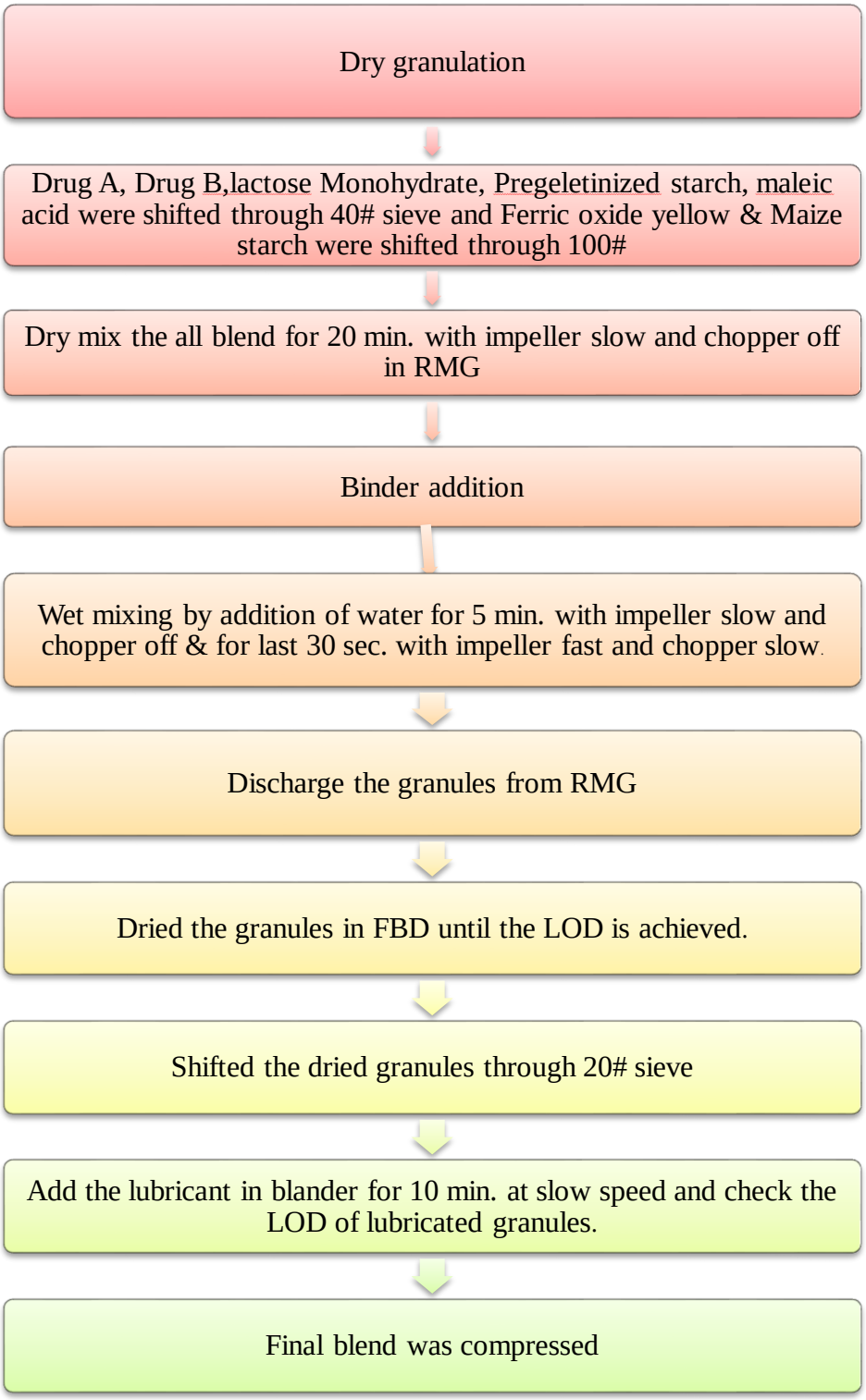


Table 4.3 In-process parameter.

Sr. No.	Parameter				
	Operations	**Temp.**	**Time (mins)**	**Impeller Speed (RPM)**	**Chopper Speed (RPM)**
1	Dry mix	--	15 mins	1400 (slow)	off
2	Binder addition	--	15 mins	1400 (slow)	off
3	Wet mixing	--	5 mins	1400 (slow)	off
4	Drying	55°C	--	--	--

4.4.3 Pre-compression evaluation parameters

4.4.3.1. Bulk density:

Bulk density is defined as a mass of a powder divided by the bulk volume. A blend sample (30 gm) was introduced in 100 ml graduated cylinder. The volume of the material was noted on graduated cylinder. The bulk density was calculated in gm/cm3 by the formula given below;

Bulk density (ρ) = M/Vo

Where, M = Mass of the powder

Vo = Volume of the powder

4.4.3.2. Tapped density:

The blend sample under test was screened through sieve no. 18 and the weight of sample equivalent to 20 gm was filled in 100 ml graduated cylinder. The tapping of the cylinder was carried out for 10, 500, and 1250 times using Bulk Density Apparatus and the tapped volume Vf was noted. The tapped density was calculated in gm/cm3 by the formula;

Tapped density (ρ) = M/Vt

Where, M = Weight of sample powder taken

Vt= Tapped volume

4.4.3.3. Compressibility index & Hausner's Ratio:

The compressibility index and Hausner ratio are measures of the property of powder to be compressed.

Table 4.4 Flow property

Sr. No.	Compressibility index (%)	Hausner ratio	Flow Character
1	<10	1.00-1.11	Excellent
2	11-15	1.12-1.18	Good
3	16-20	1.19-1.25	Fair
4	21-25	1.26-1.34	Passable
5	26-31	1.35-1.45	Poor
6	32-37	1.46-1.59	Very poor
7	>38	>1.60	Very, very poor

Carr's compressibility index and Hausner's ratio can be calculated as follows:

Carr's index = Tapped density - Bulk density / Tapped density X 100

Hausner's ratio = Tapped density / Bulk density

4.4.3.4 Determination of flow property:

The angle of repose of final blend was determined using repose graph.

Angle of repose can be calculated by using following formula:

$$\tan \theta = h/r$$

Where,

h = Height of heap in cm.

r = Radius of heap in cm.

Table 4.5 Correlations between Angle of Repose & Flow Property:

Sr. No.	Angle of Repose, Ɵ	Flow Property
1	< 25	Excellent
2	25-30	Good

3	35-40	Fair
4	41-45	Passable
5	46-55	Poor
6	56-65	Very poor
7	>66	Very, very poor

4.4.4. Evaluation of Post-Compression Parameter:

Tablets of the prepared batches were evaluated for following official and unofficial in-process parameters.

4.4.4.1 Appearance:

The general appearance and elegance of tablet was identified visually, which include tablet size, shape, color, presence or absence of an odor, taste, surface texture etc.

4.4.4.2 Weight variation:

Twenty tablets were weighed individually and average weight was determined. The individual tablet weight was compared with average tablet weight

Percentage deviation allowed under weight variation test

Table 4.6 Average weight specification

Sr. No.	Average weight of Tablets (mg) for USP	Average weight of Tablets (mg) for IP & BP	Percentage deviation
1	130 or less	80 or less	10%
2	130-324	81-250	7.5%
3	More than 324	250 or above	5%

4.4.4.3Thickness:

Ten tablets were selected randomly from each batch and thickness was measured by using digital Vernier caliper. Thickness was measured in mm for all batches.

4.4.4.4Hardness:

Hardness of the tablets was measured using schleuniger hardness tester. For each batch ten tablets were tested. The hardness was measured in Newton (N) for tablets of each batch.

4.4.4.5 Disintegration time:

The disintegration time of the tablets was determined using disintegration test apparatus. For this six tablets were introduced into each of the cylinder of the apparatus and test carried out and disintegration time noted down. The disintegration time was measured in min/sec for tablets of each batch.

4.4.4.6 Friability:

Twenty tablets were weighed and placed in the friabilator and apparatus was rotated at 25 rpm and friability were measured at 100 revolutions. After revolutions the tablets were dedusted and weighed again.

The percentage friability was measured using the formula,

% F = W initial – W final x 100

Where, % F = Friability in percentage

W initial = Initial weight of tablet

W final = Weight of tablets after revolution

4.4.4.7 In-vitro release study:

- In-vitro release profile studies of IR Tablets were carried out using USP type II dissolution apparatus due to its acceptance as standard procedure for tablet formulations.
- Water was selected as dissolution media because it was the media used by innovator and in official pharmacopeia from this combination.
- 900ml of media is used for the dissolution studies which very well achieve the sink condition.
- 75 rpm was selected as the suitable rpm.
- In-vitro dissolution of batch F1 to F3 was not performed due to sticking and capping problem.

4.4.4.8 Similarity factor (f2)

Tablet was kept in a flask having paddle and paddle were rotated at75 rpm.

Similarity factor (f2) demonstrates the similarity in the percent (%) dissolution of test product with reference product.

Dissolution profiles are considered similar if the calculated f2 value is between 50 and 100.

The similarity factor (f) is a logarithmic reciprocal square root transformation of one plus the mean squared (the average sum of squares) difference of drug percent dissolved between the test and reference products.

$f2 = 50 \cdot \log \{[1+(1/n)\sum t=1n (Rt - Tt)2]-0.5 \cdot 100\}$

4.4.4.9Stability studies

FDA and ICH specifies the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human use.

4.7 Stability study specification

Sr. No.	Study	Storage Condition	Time Period
1	Long term	25°c±2°c/60% RH±5% . RH or 30°c±2°c/65% RH±5% RH	12 month
2	Intermediate	30°c±2°c/65% RH±5% RH	6 month
3	Accelerated	40°c±2°c/75% RH±5% RH	6 month

The samples of optimized batch were kept under accelerated stability study for 3 months

4.4.4.10 Packaging:

20 tablets kept in white opaque HDPE 60 CC Bottles with CRC cap & induction sealing was done along with absorbent cotton.

Table 4.8 Stability protocol

Stability study (Conditions)		
40°C ± 2°C / 75 % RH ± 5% RH		
1 Month	2 Month	3Month

4.4.5.1 Formula of trial batches from F1to F4

Table 4.9 Formula of trial batches from F1to F4

Sr.no	Ingredient (mg)	Batches			
		F1	F2	F3	F4
1	Drug A	20.00	20.00	20.00	20.00
2	Drug B	12.5	12.5	12.5	12.5
3	Lactose monohydrate	130.10	130.10	130.10	130.10
4	Pregelatinized starch	10.00	10.00	10.00	10.00
5	Maleic Acid	10.00	10.00	10.00	10.00
6	Iron oxide yellow	1.40	1.40	1.40	1.40
Binding agent					
7	Water	q.s	q.s	q.s	q.s
Lubrication					
8	Dried maize starch	10.00	5.00	10.00	10.00

9	Sodium steary fumarate (Rank)	4.00	6.00	---	---
10	Sodium steary fumarate (Taiwan)	---	--	--	6.00
11	Magnesium stearate	---	---	2.00	---
Core weight of tablets		200 mg	200 mg	200 mg	200 mg

Trial F1

- This trial batch was take by doing compression by using sodium stearyl fumarate 2%

Table 4.10 Evaluation parameter of batch F1

Sr.no	Parameters	Observation
1.	Appearance	Sticking observed after 100 tablets
2	Hardness	40-49 N
3	Thickness	3.41-3.45 mm
4	Tablet weight	196-199 mg
5	Disintegration time	1 min 12 sec
6	Friability	0.39%

- As it was observed in trail F1, that after 100 tablets sticking was observed.
- It was assume that it may have occurred due to dried maize starch.
- Thus to overcome the problem of sticking it was decided to take the next trial by reducing the quantity of maize starch from 10 mg/tablet to 5 mg/tablet

Trial F2

- This trial batch was take by reducing the quantity of maize starch from 10 mg/tab to 5 mg/tab

Table 4.11 Evaluation parameter of batch F2

Sr.no	Parameters	Observation
1.	Appearance	Sticking observed
2	Hardness	39-47 N
3	Thickness	3.43-3.45 mm
4	Tablet weight	194-195 mg
5	Disintegration time	1 min 10 sec
6	Friability	0.25%

- As it was observed in trail F2, that even after decreasing the quantity of maize starch, the problem of sticking was not resolved.
- It was concluded that sticking was not occurring due to the quantity of maize starch.
- It was now assume that may be the problem of sticking was due to lubricating agent.
- Thus to overcome the problem of sticking it was decided to take the next trial by using only 1% magnesium stearate and not using sodium steary fumarate.

Trial F3

- This trial batch was taking by using 1% magnesium stearate.

Table 4.12 evaluation parameter of batch F3

Sr.no	Parameters	Observation
1.	Appearance	Capping was observed
2	Hardness	38-47 N
3	Thickness	3.32-3.37 mm
4	Tablet weight	200-203mg
5	Disintegration time	3 min 09 sec
6	Friability	Not performed

- As it was observed in trail F3, that by only using 1% mg.stearate the issue of sticking was solved, but capping was observed.
- It also showed that using 1% mg.stearate also increased the disintegration of the tablets
- It was concluded that 1% mg.stearate can not used in further trails as an lubricating agent.
- So it was assumed that may the issue of sticking occurring due to sodium steary fumarate .
- Thus it was decided to take the next trail using sodium steary furmarate having different vendor source.

Trial F4

- This trial batch was taken by changing the vendor source of sodium steary fumarate

Table 4.13 evaluation parameter of batch F4

Sr.no	Parameters	Observation
1.	Appearance	Sticking not observed
2	Hardness	41-55 N
3	Thickness	3.39-3.49 mm
4	Tablet weight	199.7-201.9 mg
5	Disintegration time	1 min 15 sec
6	Friability	0.20%

- As it was observed in trail F4, that by changing the source of vendor of sodium stearly fumarate the sticking and capping problem were resolved.
- Thus it was decided to reproduce the same batch in order to conform the that problem was occurring only due to sodium steary fumarate and by changing its source the problem can be solved.

4.4.5.2 Formula of trial batches from F5to F8

Table 4.14 Formula of trial batches from F5to F8

Sr.no	Ingredient (mg)	Batches			
		F5	F6	F7	F8
(mg/tab)					
1	Drug A	20	20	20	20
2	Drug B	12.5	12.5	12.5	12.5
3	Lactose monohydrate	130.10	130.10	130.10	130.10
4	Pregelatinized starch	10.00	10.00	10.00	10.00
5	Maleic Acid	10.00	10.00	10.00	10.00

6	Iron oxide yellow	1.40	1.40	1.40	1.40
Binding agent					
7	Water	q.s	q.s	q.s	q.s
Lubrication					
8	Dried maize starch	10.00	10.00	10.00	10.00
9	Sodium steary fumarate (Rank)	---	5.00	10.00	12.00
10	Sodium steary fumarate (Taiwan)	4.00	---	---	---
11	Magnesium stearate	---	---	---	---
Core weight of tablets		200 mg	200 mg	200 mg	200 mg

Trial F5

- This trial batch was to reproduce trail batch F4

Table 4.15 Evaluation parameter of batch F5

Sr.no	Parameters	Observation
1.	Appearance	Sticking not observed
2	Hardness	45-54 N
3	Thickness	3.43-3.49 mm
4	Tablet weight	199.7-201.9 mg
5	Disintegration time	1 min 41 sec
6	Friability	0.28%

- As it was observed in trail F5, that all parameter were within limit.
- Thus it was decided to take the next trial batch by increasing the quantity of sodium steary fumarate up 4% to study its effect on formulation.

Trial F6

- This trial batch was taken by increasing quantity of sodium steary fumarate up 4%

Table 4.16 evaluation parameter of batch F6

Sr.no	Parameters	Observation
1.	Appearance	Sticking not observed
2	Hardness	41-55 N
3	Thickness	3.39-3.49 mm
4	Tablet weight	199.7-201.9 mg
5	Disintegration time	1 min 15 sec
6	Friability	0.20%

- As it was observed in trail F6, that all parameter were within limit.
- Thus it was decided to take the next trial batch by increasing the quantity of sodium steary fumarate up 5 % to study its effect on formulation.

Trial F7

- This trial batch was taken by increasing quantity of sodium steary fumarate up 5%

Table 4.17 Evaluation parameter of batch F7

Sr.no	Parameters	Observation
1.	Appearance	Sticking not observed
2	Hardness	41-47 N
3	Thickness	3.44-3.45 mm
4	Tablet weight	200.9-203.9 mg
5	Disintegration time	1 min 21 sec
6	Friability	0.31%

- As it was observed in trail F7, that all parameter were within limit.

- Thus it was decided to take the next trial batch by increasing the quantity of sodium steary fumarate up 6 % to study its effect on formulation.

Trial F8

- This trial batch was taken by increasing quantity of sodium steary fumarate up 6%

Table 4.18 Evaluation parameter of batch F8

Sr.no	Parameters	Observation
1.	Appearance	Sticking not observed
2	Hardness	37-45 N
3	Thickness	3.53-3.55mm
4	Tablet weight	205.7-208.3 mg
5	Disintegration time	1 min 54 sec
6	Friability	0.41%

- As it was observed in trail F8, that all parameter were within limit.
- Thus it was observed than increasing the quantity of lubricant causes increase in disintegration time and can also increase in weight variation.

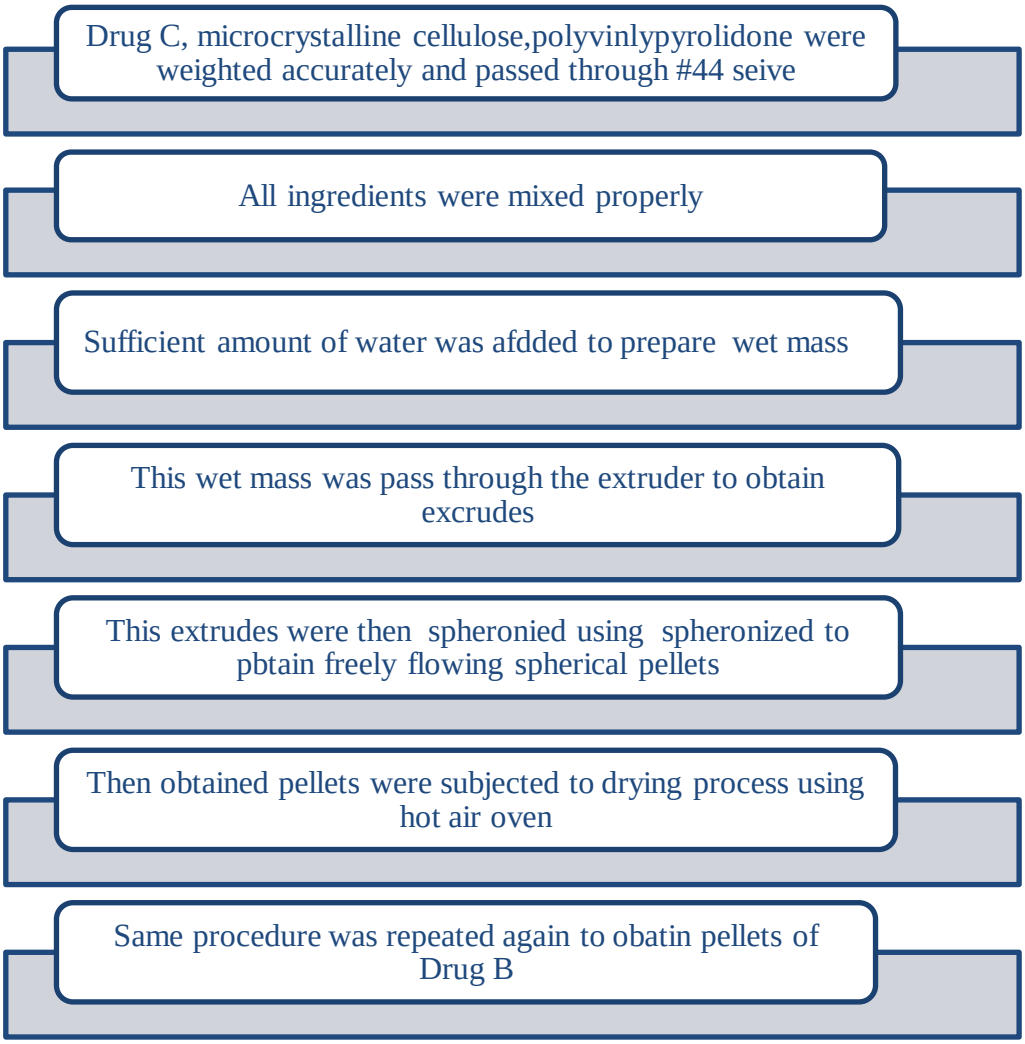
4.5 FORMULATION AND EVALUATION OF IR PELLETS

The technique used for making pellets was *extruder-spheronizer*

4.5.1 List of ingredient used in final formula

Sr.no	Ingredient	Function
1	Drug C	Anti-hypertensive agent
2	Drug B	Anti-hypertensive agent
3	MCC	Diluent
4	PVP	Binder
5	Crosspovidone	Disintigrant

4.5.2 Manufacturing process



4.5.3 Formula of IR pellets

Parameters to be optimized

1. Formulation parameter
   -effect of solvent
   -effect of disintegrating agent
2. Process parameter
   -speed of spheronizer

Formula of batch A1 –B3

1. Effect of solvent:-

Table 4.19 Formula of batch A1 –B3

Sr. no	Ingredient	QTY TAKEN					
		Batches					
		A1	A2	A3	B1	B2	B3
1	Drug C	80 mg	80 mg	80 mg	---	---	---
2	Drug B	---	---	---	12.5 mg	12.5 mg	12.5 mg
2	MCC	67%	67%	67%	67%	67%	67%
3	Cross povidone	10%	10%	10%	10%	10%	10%
4	PVP	3%	3%	3%	3%	3%	3%
5	Water	10 ml	20 ml	30 ml	10 ml	20 ml	30 ml

Observation

Sr..no	Batches	Observation
1	A1	More fines and uneven pellets formed
2	A2	Spherical pellets obtained.
3	A3	Agglomerate obtained
4	B1	More fines and uneven pellets formed
5	B2	Spherical pellets obtained.
6	B3	Agglomerate obtained

Table 4.20 Observation table of batch A1 to B3

- From all trails it was observed that 20 ml of water was considered as optimum amount of water as spherical pellets were obtained using 20 ml of water.
- Thus 20 ml of water was optimized for further trail batches

Formula of batch A4 –B6

2. Effect of speed of spheronizer

Table 4.21 Formula of batch A4 –B6

Sr. no	Ingredient	QTY TAKEN					
		Batches					
		A4	A5	A6	B4	B5	B6
1	Drug C	80 mg	80 mg	80 mg	---	---	---
2	Drug B	---	---	---	12.5 mg	12.5 mg	12.5 mg
2	MCC	67%	67%	67%	67%	67%	67%
3	Cross povidone	10%	10%	10%	10%	10%	10%
4	PVP	3%	3%	3%	3%	3%	3%
5	Water	20 ml	20 ml	20 ml	20 ml	20 ml	20 ml
Spheronizer speed (rpm)		5000	7000	8000	5000	7000	9000

Observation

Sr..no	Batches	Observation
1	A4	Pellets of larger size were formed
2	A5	Uneven size pellets obtained
3	A6	Even spherical pellets obtained
4	B4	Pellets of larger size were formed
5	B5	Uneven size pellets obtained
6	B6	Even spherical pellets obtained

Table 4.22 Observation table of batch A4 to B6

- From all trails it was observed that 9000 rpm of was considered as optimum speed of spheronized as spherical pellets of desired size were obtained using this speed
- Thus 9000 rpm was optimized as speed of spheronized for further trail batches.

Formula of batch A7 –B10

3. Effect of disintegrating agent

Table 4.23 Formula of batch A7 –B10

Sr. no	Ingredient	QTY TAKEN							
		Batches							
		A7	A8	A9	A10	B7	B8	B9	B10
1	Drug C	80 mg	80 mg	80 mg			---	----	----
2	Drug B	---	---	---	---	12.5 mg	12.5 mg	12.5 mg	12.5 mg
2	MCC	67%	62%	57%	52%	67%	62%	57%	52%
3	Cross povidone	10 %	15 %	20 %	25%	10%	15%	20%	25%

4	PVP	3%	3%	3%	3%	3%	3%	3%	3%
5	Water	20 ml	20 ml	20 ml	20 ml	20 ml	20 ml	20 ml	20 ml
speed of spheronizer (rpm)		9000	9000	9000	9000	9000	9000	9000	9000

Observation

Sr..no	Batches	Observation
1	A7	DT was observed on higher side
2	A8	DT was observed on higher side
3	A9	DT was reduced
4	A10	Optimum DT was obtained
5	B7	DT was observed on higher side
6	B8	DT was observed on higher side
7	B9	DT was reduced
8	B10	Optimum DT was obtained

Table 4.24 Observation table of batch A7 to B10

- From all the above trails it was observed that 25% disintegrating agent was giving desire DT, thus it was optimized for final batch.

Formula of optimized batch A11 –B11

Table 4.25 Formula of optimized batch A11 and B11

Sr. no	Ingredient	QTY TAKEN	
		Batches	
		A11	B11
1	Drug C	80 mg	---
2	Drug B	---	12.5mg
2	MCC	52%	52%
3	Cross povidone	25%	25%
4	PVP	3%	3%
5	Water	20 ml	20 ml
speed of spheronizer(rpm)		9000	9000

- From the above trail all parameter were found to be within limit and this batch was kept for further stability study.

4.5.4 Evaluation parameters of pellets

1. **Size distribution**

- Pellets size was determined by sieve shaking method. The most widely used method for measuring particle size distribution is sieve shaking method.
- 5gm of pellets were weight accurately and were passed through mechanical sieve shaker having sieve range from #10 mesh size to #100 mesh sizes and the amount of pellet retained on each sieve was calculated.

2. **Flow property**

- The flow property was measure by angle of repose of drug loaded pellets using fixed base cone method.
- Pellets were allowed to fall freely through a funnel fixed at 1 cm above the horizontal flat surface until the apex of the conical pile just touched to the tip

of the funnel. The height and diameter of the cone were measured and angle of repose was calculated using following formula. Each experiment was carried out in triplicate.

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

Where h = Height of pile
r = Radius of pile

3. Carr's index

Carr's index was calculated by formula

$$CI\ (\%) = \frac{pt - pb}{pt} \times 100 \quad \ldots(2)$$

4. Hausner's ratio (HR)

Hausner's ratio was calculated using measured values of bulk density and tapped density as follows:

$$HR = \frac{pt}{pb} \quad \ldots(3)$$

5. Friability testing

- The friability study was performed on the pellets to ensure their mechanical strength. Pellets of known weight were placed in a Roche Friability tester and subjected to impact at 25 rpm for 4 min. The friability was calculated using the following equation;

Friability (%) = [1– initial weight / weight retained after 100 rotations] × 100 ...(4)

6. Disintegration time

- The disintegration time of the tablets was determined using disintegration test apparatus. For this capsule filled with pellets were introduced into each of the

cylinder of the apparatus and test carried out and disintegration time noted down. The disintegration time was measured in min/sec for tablets of each batch

7. Drug content

- Drug content of the prepared pellets was determined spectrophotometer at 249 nm and 271 nm Drug C and Drug B -loaded pellets were crushed in a mortar and an amount an equivalent to 80 mg and 12.5 mg of valsartan and Hctz was dispersed in 100-ml volumetric flask containing methanol. It was further diluted with phosphate buffer (pH 6.8) and volume was made upto 100 ml. The solution was filtered and was measured at 249 nm and 271 nm.

8. In-vitro dissolution

- The release measurements were performed using USP dissolution apparatus I (Basket type) at 50 rpm.

- The test was performed using 1000 ml of phosphate buffer (pH 6.8) at 37 ± 0.5 °C. An accurately weighed amount equivalent to 80 mg and 12.5 mg of valsartan and Hctz prepared pellets were filled in hard gelatine capsule and were placed in dissolution apparatus.

- Finally the dissolution of pellets was done in phosphate buffer pH 6.8 for 2 hrs.

- Aliquotes of 5 ml was withdrawn at specific time interval (5,10, 15,30,45,60,90,120 mins) and replaced with the same amount of fresh dissolution medium. The sample was analysed uv spectroscopy at 249 nm and 271and cumulative percentage drug release was calculated.

CHAPTER 5

RESULT AND DISCUSSION

5 .1 Preformulation studies:

5.1.1 Characterization of the Drug:

5.1.1.1 Organoleptic properties:

Drug A, Drug B, Drug C was studying for organoleptic characters such as color, odor and appearance.

5.1 Physical parameter of drugs

Sr. no	Parameters	Observation		
		Drug A	Drug B	Drug C
1	Color	White powder	Off white powder	White powder
2	Odor	Odorless	Odorless	Odorless
3	Appearance	White crystalline powder	White crystalline powder	White puffy powder

Table 5.1 Physical parameter of drugs

- Results of Organoleptic properties of Drug A, Drug B, Drug C were found to be similar as mentioned in the literature.

5.1.1.2 Solubility:

The solubility of drug was determined as per BCS Class-II and Class-III. Solubility of the drug were determined in 5 different media along the pH rang 1 to 7.5. These media were water, 0.1 N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer & pH 7.5 phosphate buffer.

Table 5.2 solubility parameter of drugs

Sr.no	Media	Solubility(mg/ml)		
		Drug A	Drug B	Drug C
1	water	0.058	0.051	0.045
2	0.1 N HCl	0.071	0.032	0.037
3	pH 4.5 acetate buffer	0.046	0.079	0.045
4	pH 6.8 phosphate buffer	0.065	0.073	0.074

5	pH 7.5 phosphate buffer	0.056	0.0023	0.034

5.1.1.3 Melting point:

The melting point was determined by melting point apparatus and the corrected melting point was found as following.

Table 5.3 Melting point of drugs

Sr.no	Sample	Observed melting point	Reported standard
1	Drug A	144 ^{0}C	146 ^{0}C
2	Drug B	272 °C	273–275 °C
3	Drug C	114°C	116-117 °C

5.1.1.4 UV spectroscopy study:

The spectrum is shown in figure Wavelength of maximum absorbance (λmax) in methanol as a solvent.

Table 5.4 Uv spectroscopy of drugs

Sr.no	Sample	Observed λ max
1	Drug A	206 nm
2	Drug B	272 nm
3	Drug C	249 nm

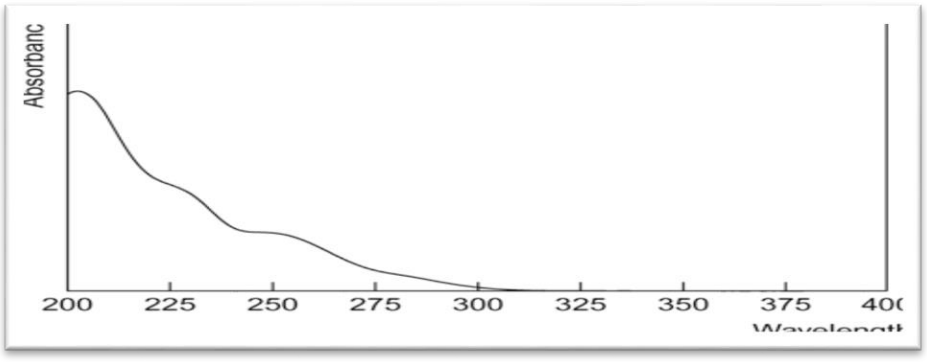


Fig 5.1 Uv spectra of Drug C

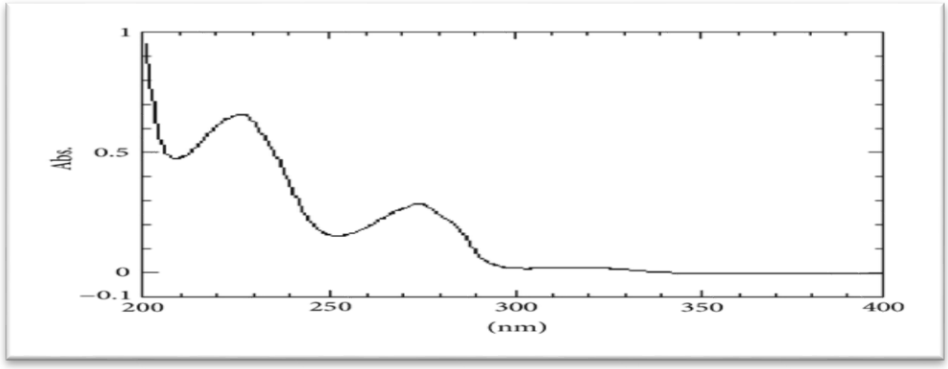


Fig 5.2 Uv spectra of Drug B

5.1.1.4 Calibration curve

- Calibration curves of Drug A, Drug B, Drug C in methanol and 6.8 phosphate buffers.
- The calibration curve of Drug A was performed in methanol.

Table 5.5 calibration curve of drug A

Sr.no	Concentration (µg/ml)	Absorbance (206 nm)
1	2	0.106
2	4	0.212
3	6	0.321
4	8	0.435
5	10	0.534
6	12	0.632
7	14	0.733
8	16	0.819
9	18	0.921
10	20	0.989

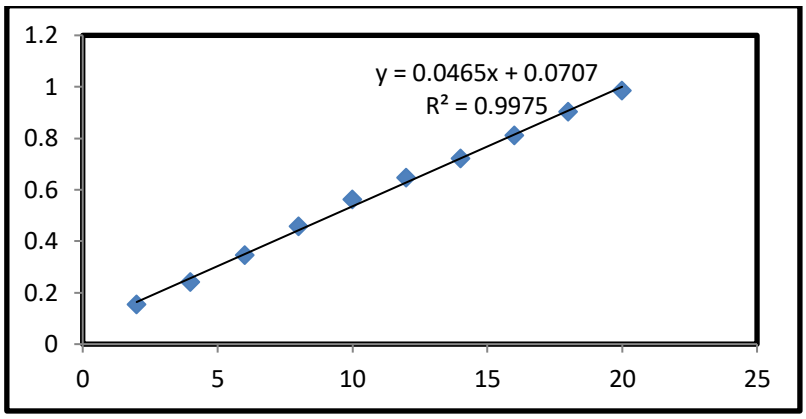


Fig 5.3 calibration curve of Drug A in methanol

The calibration curve was found to be linear in the concentration range of 2-20 µg/ml having a coefficient of regression value R2 = 0.9976 and line equation, y = 0.0497x + 0.0238.

- The calibration curve of Drug B was performed in methanol.

Table 5.6 calibration curve of drug B

Sr.no	Concentration (µg/ml)	Absorbance (272 nm)
1	2	0.156
2	4	0.243
3	6	0.345
4	8	0.456
5	10	0.547
6	12	0.623
7	14	0.743
8	16	0.819
9	18	0.921
10	20	0.989

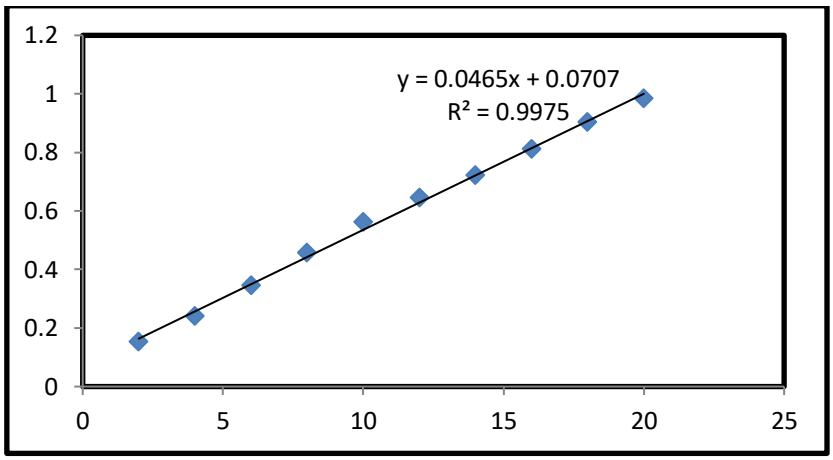


Fig 5.4 calibration curve of Drug B in methanol

- The calibration curve was found to be linear in the concentration range of 2-20 µg/ml having a coefficient of regression value R2 = 0.9983 and line equation, y = 0.0471x + 0.0659
- The calibration curve of Drug C was performed in 6.8 phosphate buffer.

Table 5.7 calibration curve of Drug C

Sr.no	Concentration (µg/ml)	Absorbance (249 nm)
1	2	0.144
2	4	0.263
3	6	0.356
4	8	0.461
5	10	0.571
6	12	0.634
7	14	0.745
8	16	0.821
9	18	0.903
10	20	0.987

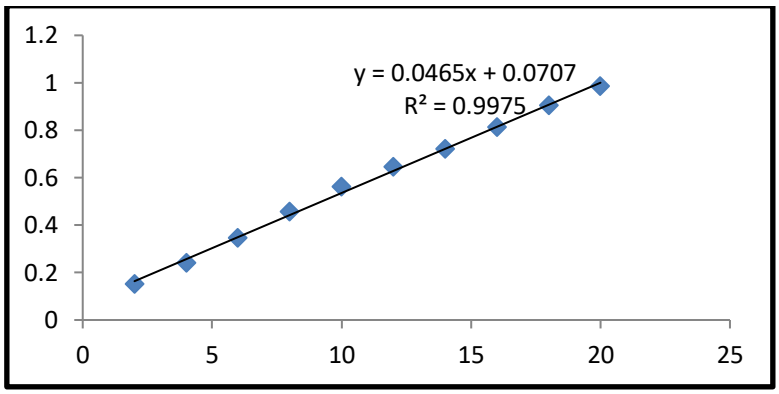


Fig 5.5 calibration curve of Drug C in methanol

- The calibration curve was found to be linear in the concentration range of 2-20 µg/ml having a coefficient of regression value R2 = 0.9965 and line equation, y = 0.0464x + 0.078

5.1.1.6 FT-IR spectrum of Drug A: The FTIR spectra of pure Drug A showed peaks in wave numbers (cm-1) which corresponds to the functional group present in the structure of the drug. FT-IR spectrum of Drug A is shown in figure

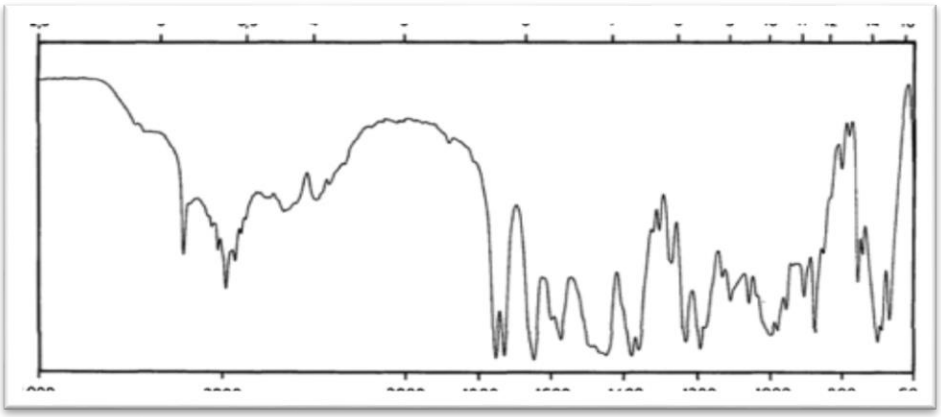


Fig.5.6 FTIR spectra of Drug A

Table 5.8 Result of FTIR spectra of Drug A

Sr. No	Group	Range (cm^{-1})
1	C=C stretch	1680-1640 cm^{-1}
2	=C–H stretch	3100-3000 cm^{-1}
3	=C–H bend	1000-650 cm^{-1}
4	C–O stretch [1]	1260-1050 cm^{-}
5	C=O stretch	1715 cm^{-1}
6	O–H	3300-2500 cm^{-1}
7	N–O symmetric stretch	1360-1290 cm^{-1}

5.1.1.6 FT-IR spectrum of Drug B : The FTIR spectra of pure Drug A showed peaks in wave numbers (cm-1) which corresponds to the functional group present in the structure of the drug. FT-IR spectrum of Drug B is shown in figure

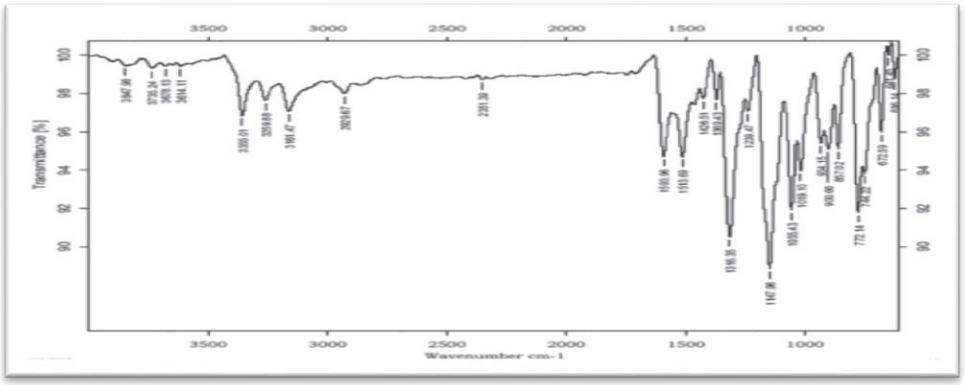


Fig.5.7 FTIR spectra of Drug B

Table 5.9 Result of FTIR spectra of Drug B

Sr. No	Group	Range (cm^{-1})
1	C–Cl stretch	850-550 cm^{-1}
2	N–O asymmetric stretch [1]	1550-1475 cm^{-}
3	C–H stretch	100-3000 cm^{-1}

5.1.1.7 Differential scanning Calorimetry (DSC) study of Drug A:

The DSC curve of Drug A showed a sharp endothermic peak (Tpeak = 143.3°C) corresponding to its melting point, indicating its crystalline nature.

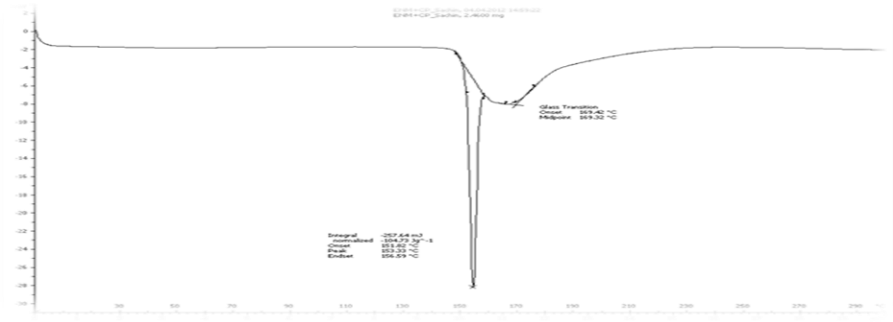


Fig 5.8 DSC of Drug A

5.1.1.8 X RPD data

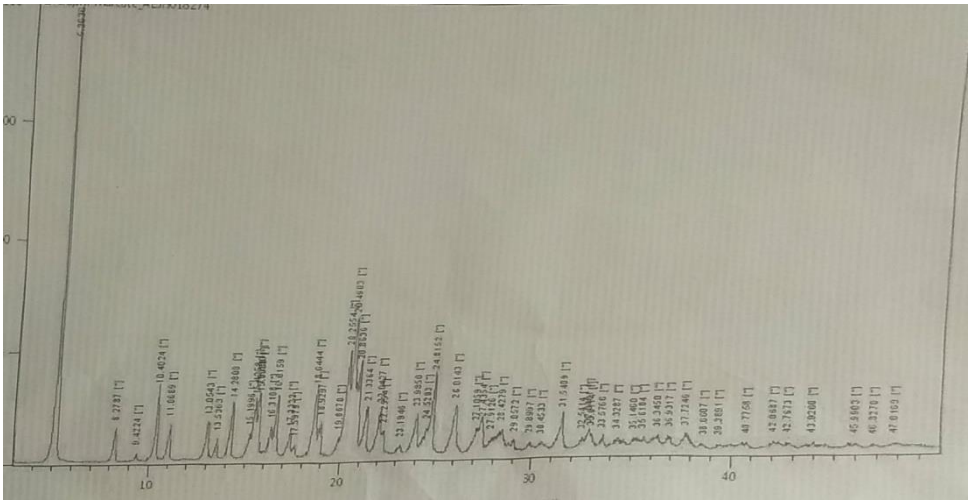


Fig 5.9 XRPD Pure drug A

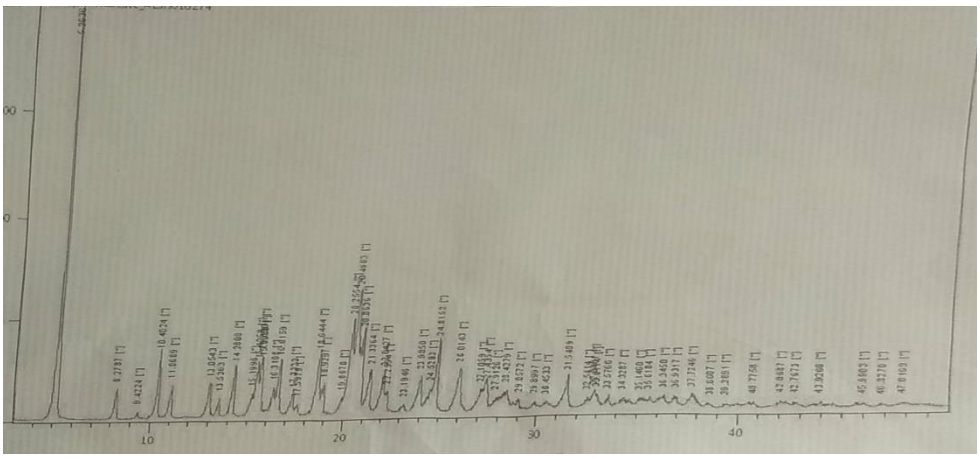


Fig 5.10 XRPD Pure drug B

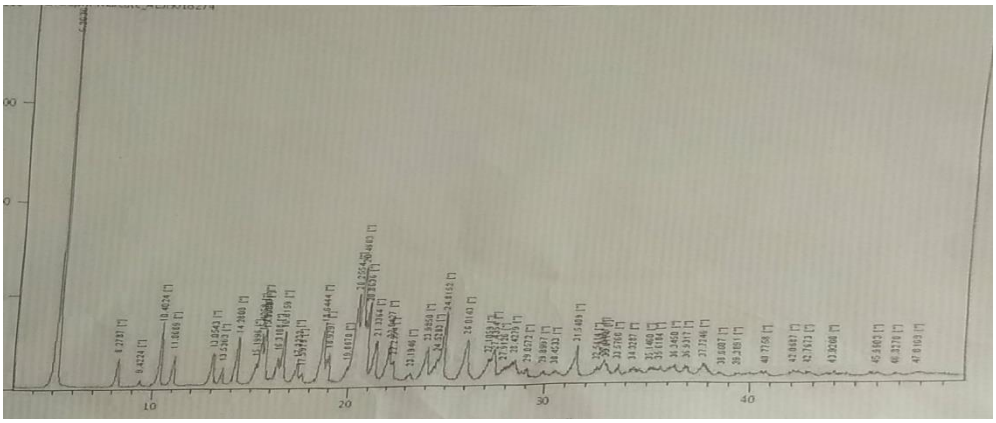


Fig 5.11 XRPD of finished product

The X- RPD graph explains that there is no any change was observed after compression and the excipients are compatible with API

5.1.1.9 Particle size analysis

Table 5.10 Particle size distribution For Drug A

Sr.no	Particle size distribution	size
1	D10 NMT 10 µm	Less than 5.90 µm
2	D50 NMT 15 µm	Less than 11.89 µm
3	D90 NMT 20 µm	Less than19.70 µm

From the above table it is observed D90 means 90% of the given DRUG A particles are smaller than 20 µm

Table 5.11 Particle size distribution For Drug B

Sr.no	Particle size distribution	Size
1	D10 NMT 10 µm	Less than 5.561 µm
2	D50 NMT 15 µm	Less than 11.618 µm
3	D90 NMT 25 µm	Less than22.712µm

From the above table it is observed D90 means 90% of the given DRUG B particles are smaller than 25 µm.

5.1.1.10 Solid State Compatibility Studies of Drug with Excipients:

Table 5.12 Physical observations of drugs for compatibility study.

Sr.no	Sample	Initial	After 3 months
1	Drug A	No physical change	No physical change
2	Drug B	No physical change	No physical change
3	Drug C	No physical change	No physical change

Drug substance excipients compatibility study was carried out to find out the suitability of the excipients

Sr no.	**Sample**	**Observation**		**Ratio**
		Initial	40°C/75% RH(2 month)	
1	Drug A	White to off white	No change	--
2	Drug B	White to off white	No change	--
3	Drug A+Lactose monohydrate	White to off white	No change	1:10
4	Drug B	White to off white	No change	1:10

	+Lactose monohydrate			
5	Drug A +Pregelatinised starch	White to off white	No change	1:10
6	Drug B+Pregelatinised starch	White to off white	No change	1:10
7	Drug A+Malelic acid	White to off white	No change	1:1
8	Drug B+Malelic acid	White to off white	No change	1:1
9	Drug A+Iron oxide yellow	Pale yellow	No change	1:0.1
10	Drug B+Iron oxide yellow	Pale yellow	No change	1:0.1
11	Drug A+Dried maize starch	White to off white	No change	1:10
12	Drug B+Dried maize starch	White to off white	No change	1:10
13	Drug A+Sodium steary fumarate	White to off white	No change	1:1
14	Drug B+Sodium steary fumarate	White to off white	No change	1:1
15	Drug A+Magnesium	White to off white	No change	1:1

	stearate			
16	Drug C+MCC	White to off white	No change	1:1
17	Drug C +PVP	White to off white	No change	1:1
18	Drug C +Crosspovidone	White to off white	No change	1:1
19	Drug B +MCC	White to off white	No change	1:1
20	Drug B +PVP	White to off white	No change	1:1
21	Drug B+Crosspovidone	White to off white	No change	1:1

From all the above result it can be concluded that the drug and exciepient were compatible with each other and can be for the formulation process.

Parameters of tablet evaluation

5.2 Pre-compression parameter

PARAMETER/POWDER BLEND:

Evaluation of density and flow properties of Drug A and Drug B:

Table 5.13 Observation of density and flow parameter

SR.NO	Density (g/cm3)	Flow properties of Drug A	Flow properties of Drug B
	Bulk	0.35	0.29
	Tapped	0.48	0.38
	Carr's index	15.79	14.71
	Hausner ratio	1.21	1.13

The above observation indicates that the drugs have good flow. It's indicates that drug material is good flow properties.

5.3 Evaluation of Innovator:

Table 5.14 Innovator evaluation

Sr. No	Parameter	Specification
1	Strength	20/12.5mg
2	Core/Coated	Core
3	Label Claim	20/12.5mg
4	Mfg. By	IPCA LAB. LTD.
5	Marketed By	IPCA LAB. LTD.
6	Specification	USP
7	Appearance	Pale yellow color, circular, biconvex uncoated tablet with "BL" embossed on one side and break line on other on other side
8	Avg. Wt.	200 mg
9	Hardness	20 N -120 N
10	Thickness	3.5 mm
11	Disintegration	Not more than 15 min
12	Shelf-life	Two Years

13	Storage	Store innovator comp in original package in order to protect from light & moisture , Do not store package above 30 °C
14	Packaging	HDPE Bottle Pack

5.4 Evaluation of pre-compression parameters of blend

Table 5.15 Evaluation of pre-compression parameters of blend.

Sr. no	Batch no.	% LOD	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index	Hausner's ratio	Flow property
1	F1	1.02	0.423	0.503	15.904	1.189125	Excellent
2	F2	1.03	0.516	0.632	18.354	1.224806	Good
3	F3	0.91	0.519	0.643	19.284	1.238921	Good
4	F4	0.99	0.513	0.651	21.198	1.269006	Good
5	F5	0.93	0.517	0.689	24.963	1.332689	Passable
6	F6	1.04	0.589	0.671	12.220	1.139219	Excellent
7	F7	1.01	0.561	0.621	9.6618	1.106952	Excellent
8	F8	0.97	0.578	0.631	8.3993	1.091696	Excellent

From the values of Hausner's ratio & Carr's Compressibility Index we concluded that granules of the above batches were having good flow property and can be proceed for the compression process.

5.5 Post compression parameters

All post compression evaluation parameters were performed and results are shown in the tablet below.

Table 5.16 (A) Evaluation of post-compression parameters

Sr. no	Batch no.	Appearance	Hardness (N)
1	F1	Sticking observed after 100 tablets	40-49
2	F2	Sticking observed	39-47
3	F3	Capping was observed	38-47
4	F4	Sticking not observed	41-55
5	F5	Sticking not observed	45-54
6	F6	Sticking not observed	41-55
7	F7	Sticking not observed	41-47
8	F8	Sticking not observed	37-45

From the above parameter it can concluded that formulation F 3 to F 8 were found to be more satisfactory as they were free from any kind of defect and their hardness was also in limit.

Table 5.16 (B) Post compression parameter for batch f1 to f8

Sr. no	Batch no.	Avg. Weight (mg)	DT	Friability (%)	Thickness (mm)
1	F1	196-199	1 min 12 sec	0.39	3.41-3.45
2	F2	194-195	1 min 10 sec	0.25	3.43-3.45
3	F3	200-203	3 min 09 sec	Not performed	3.32-3.37
4	F4	199.7-200.9	1 min 15 sec	0.20	3.39-3.49

5	F5	199.7-201.9	1 min 41 sec	0.28	3.43-3.49
6	F6	199.9-202.1	1 min 15 sec	0.20	3.39-3.49
7	F7	200.9-203.9	1 min 21 sec	0.31	3.44-3.45
8	F8	205.7-208.3	1 min 54 sec	0.41	3.53-3.55

From all the above parameter it can be concluded that all the post compression parameter were found to be satisfactory and within limit.

IN-VITRO DISSOLUTION PROFILE:

Dissolution Summary:

Medium : Dissolution Profile in water

Apparatus : Paddle

RPM : 75

Volume : 900 ml

Dissolution profiles of drug for Innovator Vs trials F4

Table 5.17 Dissolution profiles of drug for Innovator Vs trials F4

Sr.no	Time (min)	% Drug release			
		Innovator		F4	
		Drug A	Drug B	Drug A	Drug B
1	5	32	24	28	21
2	10	48	41	42	40
3	15	72	62	70	59
4	30	95	79	93	75
5	45	97	88	96	85
6	60	99	88	98	87

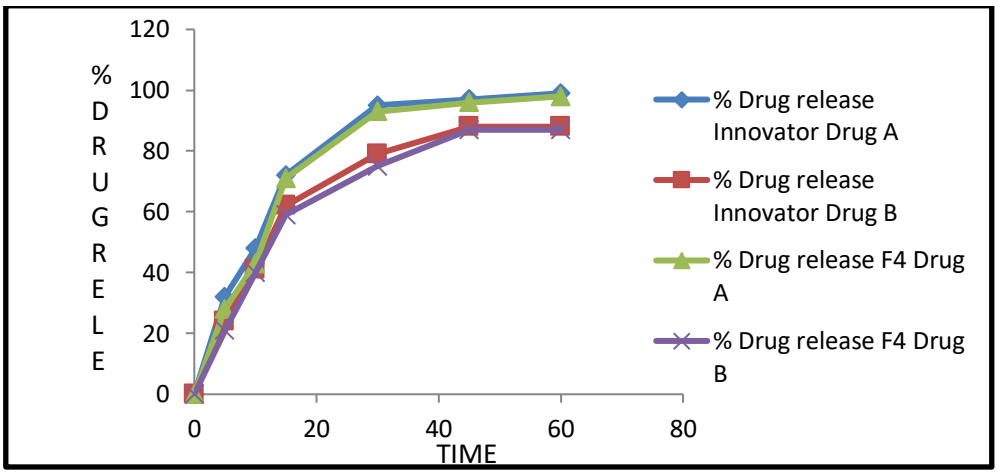


Fig 5.12 Dissolution profiles of drug for Innovator Vs trials F4

Table 5.18 Dissolution profiles of drug for Innovator Vs trials F5

Sr.no	Time (min)	% Drug release			
		Innovator		F5	
		Drug A	Drug B	Drug A	Drug B
1	5	32	24	30	20
2	10	48	41	45	37
3	15	72	62	68	56
4	30	95	79	90	72
5	45	97	88	95	83
6	60	99	88	95	85

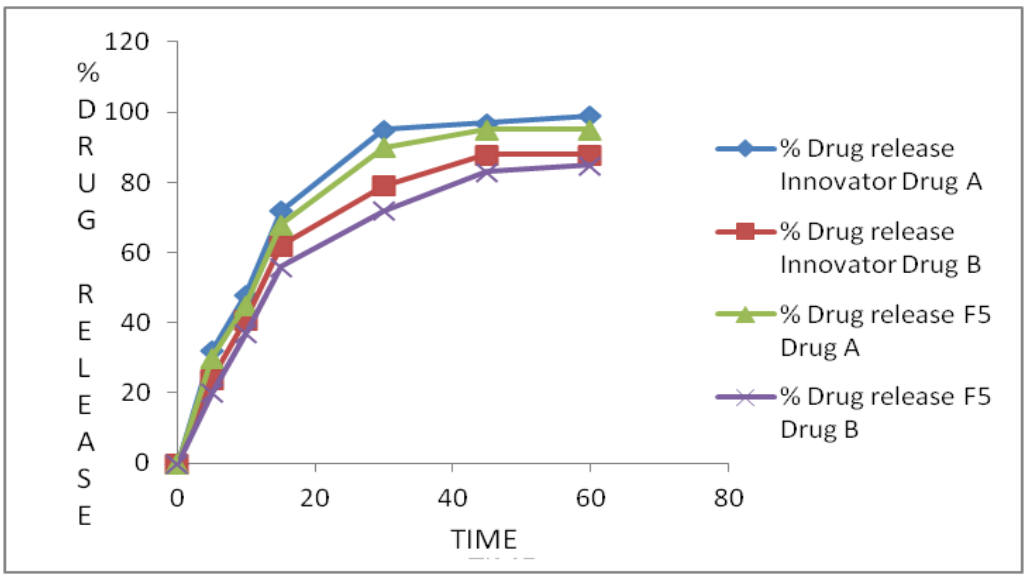


Fig 5.13 Dissolution profiles of drug for Innovator Vs trials F5

Table 5.19 Dissolution profiles of drug for Innovator Vs trials F6

Sr.no	Time (min)	% Drug release			
		Innovator		F6	
		Drug A	Drug B	Drug A	Drug B
1	5	32	24	28	24
2	10	48	41	43	36
3	15	72	62	69	54
4	30	95	79	91	72
5	45	97	88	93	82
6	60	99	88	93	83

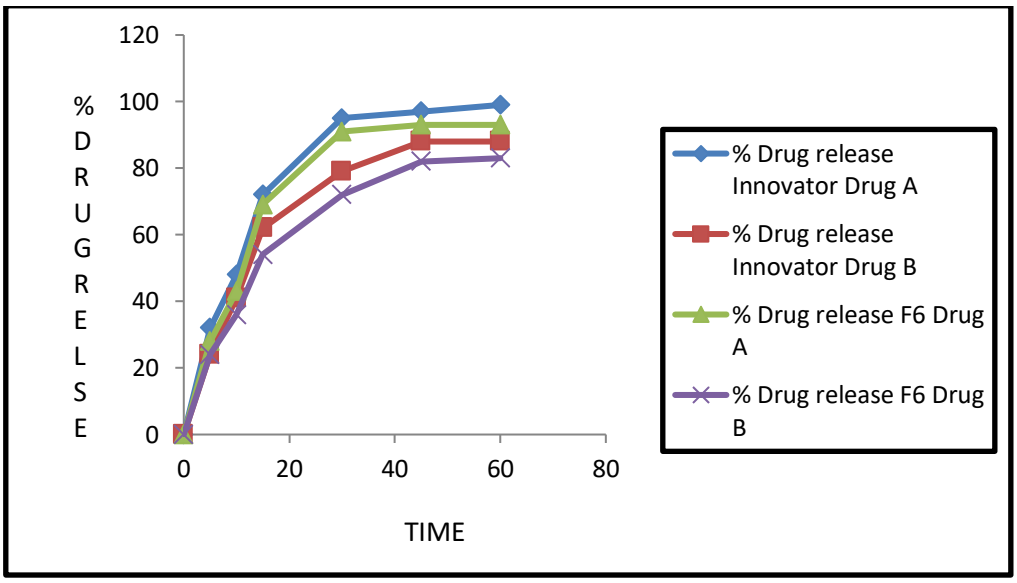


Fig 5.14 Dissolution profiles of drug for Innovator Vs trials F6

Table 5.20 Dissolution profiles of drug for Innovator Vs trials F7

Sr.no	Time (min)	% Drug release			
		Innovator		F7	
		Drug A	Drug B	Drug A	Drug B
1	5	32	24	28	24
2	10	48	41	43	36
3	15	72	62	69	54
4	30	95	79	91	72
5	45	97	88	93	82
6	60	99	88	93	83

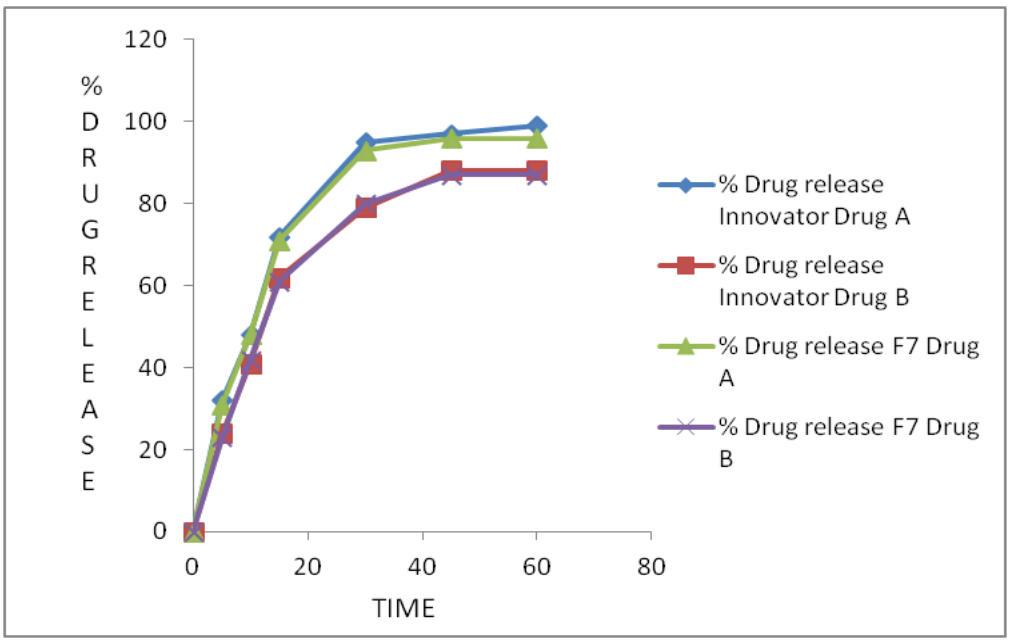


Fig 5.15 Dissolution profiles of drug for Innovator Vs trials F7

Table 5.21 Dissolution profiles of drug for Innovator Vs trials F8

Sr.no	Time (min)	% Drug release			
		Innovator		F8	
		Drug A	Drug B	Drug A	Drug B
1	5	32	24	27	20
2	10	48	41	41	35
3	15	72	62	60	50
4	30	95	79	87	69
5	45	97	88	89	74
6	60	99	88	89	74

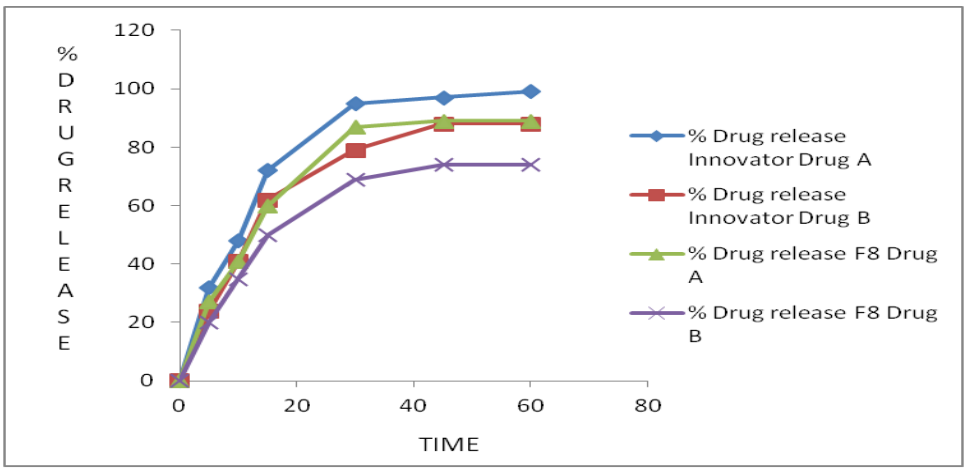


Fig 5.16 Dissolution profiles of drug for Innovator Vs trials F8

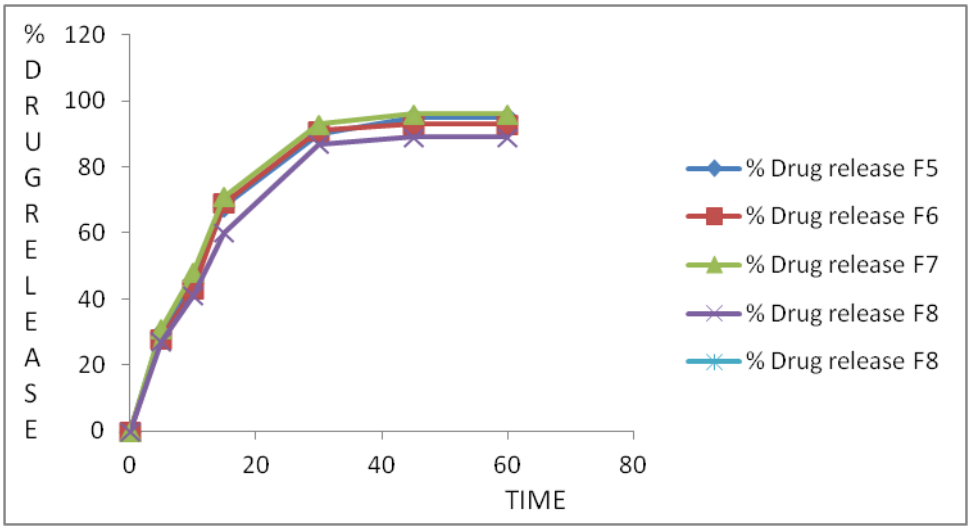


Fig 5.17 Comparison of % drug release from F4 –F8 of Drug A

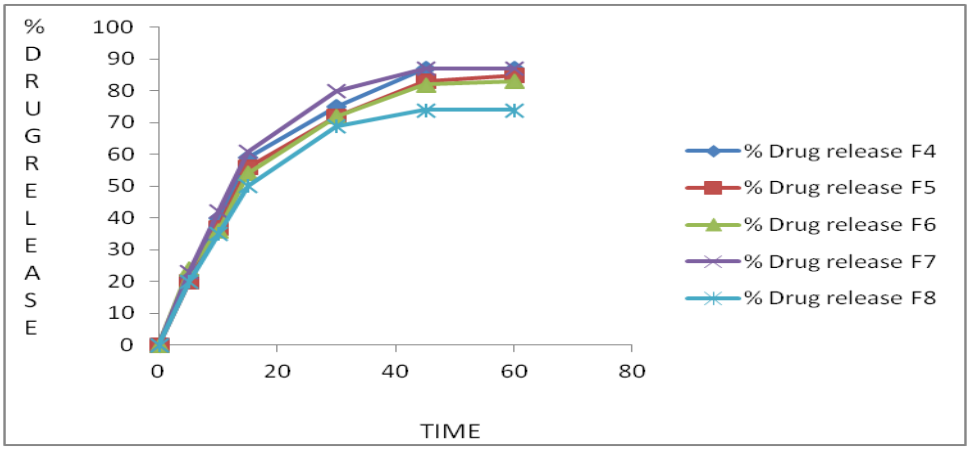


Fig 5.18 Comparison of % drug release from F4 –F8 of Drug B

From the dissolution data it was found out that F7 was found to have the most identical drug release profile as compared to the innovator. Thus batch f7 was kept for stability testing.

5.6 Container closer system

Selection of Packaging material

Tablets were kept in white opaque HDPE 60 CC Bottles with CRC cap & induction sealing was done along with absorbent cotton.

Justification: White opaque HDPE bottles provide complete protection against light, water vapor, gases etc.

5.7 Stability study

Batch No.: F7 was put on stability as below mentioned condition.

Condition: Batch F5 & F6 at 40°C ± 2°C / 75% RH ± 5 % RH

Packaging: white opaque HDPE 60 CC Bottles with CRC cap & induction sealing was done along with absorbent cotton.

Description: Pale yellow colour,circular, biconvex, uncoated tablet with " BL" embossed on one side and breakline on other side

Table 5.22 stability study data for IR tablets

SR. NO	PARAMETER	TIME	INTIAL		1 MONTH		3 MONTH	
			DR A	DR B	DR A	DR. B	DR A	DR. B
1	ASSAY	---	98 %	99.53 %	97.93 %	99.12 %	97 %	98.87 %
2	RELATED SUB.	---	0.05 %	0.10 %	0.0%	0.12%	0.10%	0.15 %
3	DISSO. MEDIA 900 ML	5	40 %	38 %	45 %	32 %	35 %	38 %
		10	54 %	56 %	52 %	48 %	58 %	51 %

	WATER 50 RPM	15	61 %	67 %	68 %	72 %	64 %	69 %
		30	99 %	83 %	96 %	81 %	97 %	81 %
		45	99 %	89 %	96 %	87 %	98%	86 %
		60	98 %	94 %	97 %	91 %	98 %	90 %
4	DT		1 min 39 sec		1min 41sec		1min 41sec	
5	HARDNESS		37-43		37-43		37-43	
6	FRIABITY		0.40%		0.40%		0.40%	
7	THCKNESS		3.34-3.50		3.34-3.50		3.34-3.50	

Discussion:

For stability study 15 tablets kept in white opaque HDPE 60 CC bottles with

CRC cap & induction sealing was done along with absorbent cotton. and the container were kept in stability chamber at 40°C ± 2°C / 75% RH ± 5 % RH.

Relative humidity for 1 & 3 months supplied by Neutronic Supplier Ltd. Mumbai. Tablets were evaluated for physical appearance, hardness, thickness, drug content, dissolution and related substance.

There is no change in description of tablet after 3 month stability study.

Total impurity was at initially 0.21% after

1 & 3 month was found to be 0.24% & 29 % which are in limit hence from the above stability data at 40°C ± 2°C / 75% RH ± 5 % RH, it reveals that the product is stable at 40°C ± 2°C / 75% RH ± 5 % RH for 12 Weeks (3 months)

5.8Evaluation parameter of IR release pellets

Table 5.23 (A) Evaluation parameters for Drug C pellets

Sr. no	Batch no.	Shape	Size distribution
1	A1	Rod shaped	1.2-2.2 mm
2	A2	Spherical.	1.2-1.8 mm
3	A3	Agglomerate	1.1-2.7 mm
4	A4	Dumbbell shaped	1.2 -2.5 mm
5	A5	Rod and dumbbell shaped	1.2-1.9 mm
6	A6	Spherical	0.8-1.2 mm
7	A7	Spherical	0.8-1.2 mm
8	A8	Spherical	0.8-1.2 mm
9	A9	Spherical	0.8-1.2 mm
10	A10	Spherical	0.8-1.2mm

From the above trial taken it was found that batch A2 was found to have spherical shaped pellets when compared to batch A1 and A3.

Batch from A6 to A10 were found to be more satisfactory in term of particle size distribution.

Table 5.23 (B) Evaluation parameters for Drug C pellets

Sr. no	Batch no.	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index	Hausner's ratio
1	A1	0.411	0.567	27.51323	1.379562
2	A2	0.414	0.467	11.34904	1.128019
3	A3	0.431	0.643	32.97045	1.491879
4	A4	0.542	0.671	19.22504	1.238007
5	A5	0.517	0.689	24.96372	1.332689
6	A6	0.589	0.791	25.53729	1.342954

7	A7	0.561	0.621	9.661836	1.106952
8	A8	0.578	0.631	8.399366	1.091696
9	A9	0.561	0.603	6.965174	1.074866
10	A10	0.523	0.612	14.54248	1.170172

From all the above parameter it can be concluded that batches from A7 to A10 were found to have excellent flow property.

Table 5.23 (C) Evaluation parameters for Drug C pellets

Sr. no	Batch no.	Disintegration time	Flow property
1	A1	7 min 41 sec	Passable
2	A2	7 min 23 sec	Good
3	A3	7 min 36 sec	passable
4	A4	8 min 04 sec	Good
5	A5	8 min 54 sec	Passable
6	A6	9 min 25 sec	Passable
7	A7	9 min 34 sec	Good
8	A8	8 min 37 sec	Good
9	A9	7 min 34 sec	Good
10	A10	7 min 03 sec	Good

From the above parameter it was concluded that formulation A9 and A10 were found to desired disintegration time with was found to be good for Ir release of formulation.

Table 5.20 (D) Evaluation parameters for Drug C pellets

Sr. no	Batch no.	Fribilty	Assay
1	A1	1.05 %	98.09 %
2	A2	0.56%	98.41%
3	A3	0.81%	99%
4	A4	0.64%	98.06%
5	A5	0.51%	99.09%

6	A6	0.49%	100.02%
7	A7	0.63%	98.56%
8	A8	0.61%	101.23%
9	A9	0.64%	99.05%
10	A10	0.52%	99.45%

From the above parameter it was concluded that assay and friability of batch A2-A9 were found to be in limit.

Table 5.24 (A) Evaluation parameters for Drug B pellets

Sr. no	Batch no.	Shape	Size distribution
1	B1	Rod shaped	1.2-2.2 mm
2	B2	Spherical.	1.2-1.8 mm
3	B3	Agglomerate	1.1-2.7 mm
4	B4	Dumbbell shaped	1.2 -2.5 mm
5	B5	Rod and dumbbell shaped	1.2-1.9 mm
6	B6	Spherical	0.8-1.2 mm
7	B7	Spherical	0.8-1.2 mm
8	B8	Spherical	0.8-1.2 mm
9	B9	Spherical	0.8-1.2 mm
10	B10	Spherical	0.8-1.2mm

From the above trial taken it was found that batch B2 was found to have spherical shaped pellets when compared to batch B1 and B3.

Batch from B6 to B10 were found to be more satisfactory in term of particle size distribution.

Table 5.24 (B) Evaluation parameters for Drug B pellets

Sr. no	Batch no.	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index	Hausner's ratio
1	B1	0.411	0.567	27.51323	1.379562
2	B2	0.414	0.467	11.34904	1.128019
3	B3	0.431	0.643	32.97045	1.491879
4	B4	0.542	0.671	19.22504	1.238007
5	B5	0.517	0.689	24.96372	1.332689
6	B6	0.589	0.791	25.53729	1.342954
7	B7	0.561	0.621	9.661836	1.106952
8	B8	0.578	0.631	8.399366	1.091696
9	B9	0.561	0.603	6.965174	1.074866
10	B10	0.523	0.612	14.54248	1.170172

From the above trial taken it was found that batch B2 was found to have spherical shaped pellets when compared to batch B1 and B3.

Batch from B6 to B10 were found to be more satisfactory in term of particle size distribution.

Table 5.24 (C) Evaluation parameters for Drug B pellets

Sr. no	Batch no.	Disintegration time	Flow property
1	B1	7 min 41 sec	Passable
2	B2	7 min 23 sec	Good
3	B3	7 min 36 sec	passable
4	B4	8 min 04 sec	Good
5	B5	8 min 54 sec	Passable
6	B6	9 min 25 sec	Passable
7	B7	9 min 34 sec	Good

8	B8	8 min 37 sec	Good
9	B9	7 min 34 sec	Good
10	B10	7 min 03 sec	Good

From the above parameter it was concluded that formulation A9 and A10 were found to desired disintegration time with was found to be good for IR release of formulation.

Table 5.24 (D) Evaluation parameters for Drug B pellets

Sr. no	B1	Fribilty	Assay
1	B2	1.05 %	98.09 %
2	B3	0.56%	98.41%
3	B4	0.81%	99%
4	B5	0.64%	98.06%
5	B6	0.51%	99.09%
6	B7	0.49%	100.02%
7	B8	0.63%	98.56%
8	B9	0.61%	101.23%
9	B10	0.64%	99.05%
10	B1	0.52%	99.45%

From the above parameter it was concluded that assay and friability of batch A2-A9 were found to be in limit.

In –vitro drug release

Medium : Dissolution Profile in 6.8 phosphate buffer

Apparatus : Paddle

RPM : 75

Volume : 1000 ml

Table 5.25 Dissolution profile of A2B2 batch

Sr.no	Time (min)	% Drug release	
		A2B2	
		Drug C	Drug B
1	5	27	15
2	10	39	20
3	15	48	23
4	30	64	39
5	45	75	57
6	60	81	69
7	90	87	73
8	120	89	75

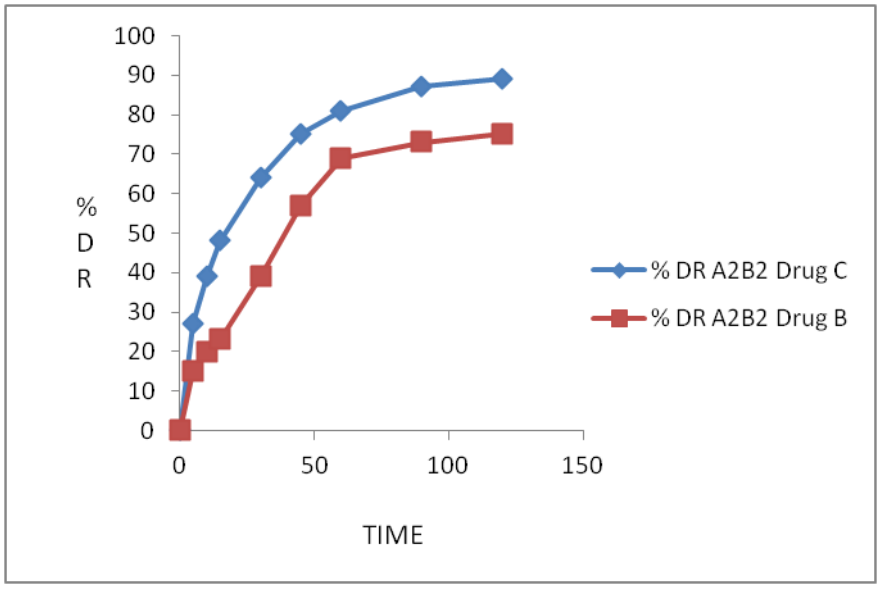


Fig 5.19 Dissolution profile of A2B2 batch

From the above dissolution profile it can be seen that less than 80% dissolution was obtained in 120 min. Thus it can be concluded that this batch failed in dissolution study.

Table 5.26 Dissolution profile of A7 B7 batch

Sr.no	Time (min)	% Drug release	
		A7B7	
		Drug C	Drug B
1	5	12.3	8.9
2	10	24	18
3	15	31	23
4	30	45	39
5	45	62	57
6	60	74	69
7	90	77	73
8	120	77	75

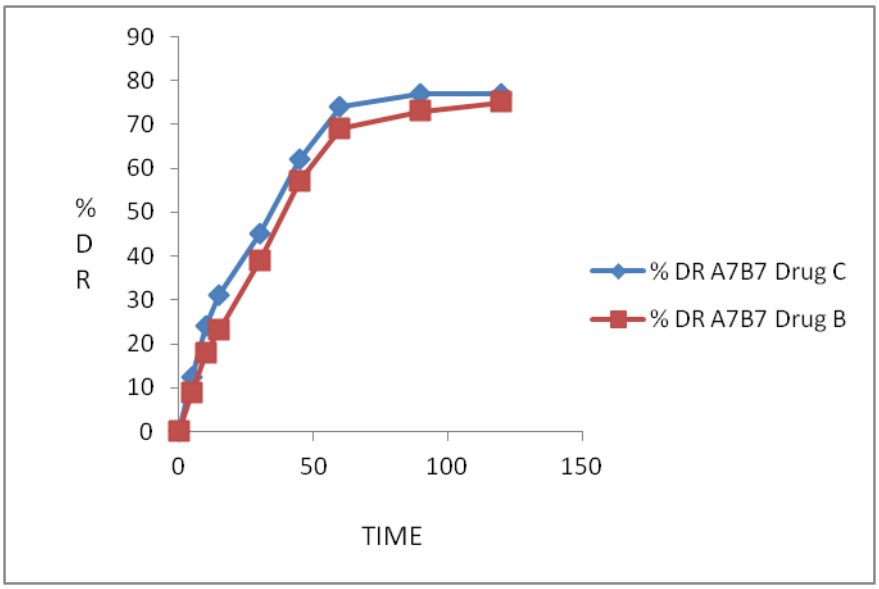


Fig 5.20 Dissolution profile of A7B7 batch

From the above dissolution profile it can be concluded that the rate of dissolution was much slower than required.

Table 5.27 Dissolution profile of A8B8 batch

Sr.no	Time (min)	% Drug release	
		A8B8	
		Drug C	Drug B
1	5	22	8
2	10	35	18
3	15	41	23
4	30	54	39
5	45	69	57
6	60	79	69
7	90	81	73
8	120	82	75

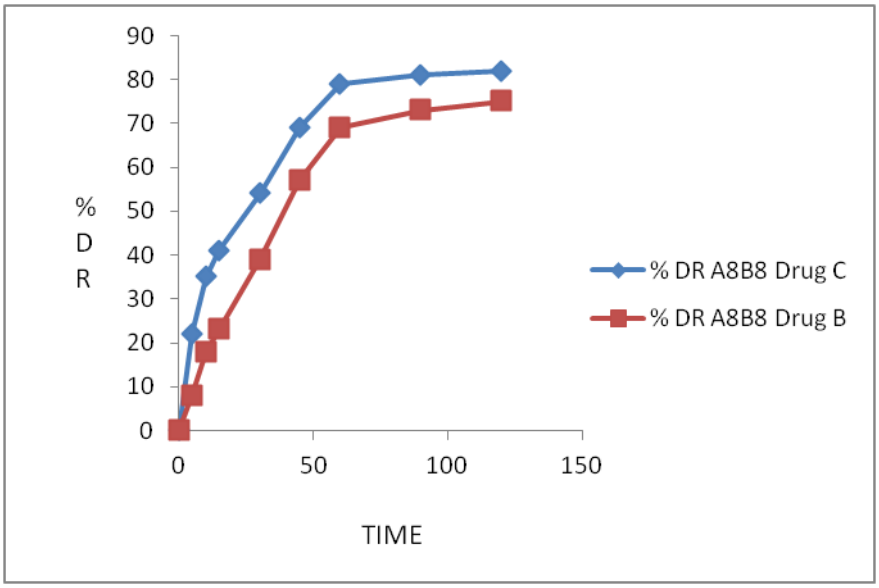


Fig 5.21 Dissolution profile of A8B8 batch

From the above dissolution profile it can be concluded that the rate of dissolution was much slower than required.

Table 5.28 Dissolution profile of A9B9 batch

Sr.no	Time (min)	% Drug release	
		A9B9	
		Drug C	Drug B
1	5	26	15
2	10	38	24
3	15	49	38
4	30	61	45
5	45	73	68
6	60	83	76
7	90	87	81
8	120	89	83

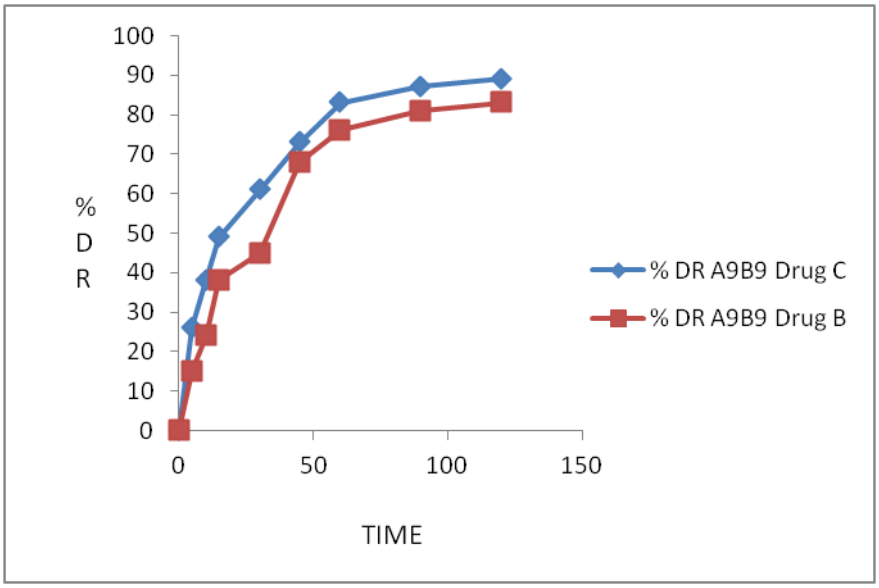


Figure 5.22 Dissolution profile of A9B9 batch

From the above dissolution profile it can be seen that by increasing the disintegration rate the dissolution has been fast.

Table 5.29 Dissolution profile of A10B10 batch

Sr.no	Time (min)	% Drug release	
		A10B10	
		Drug C	Drug B
1	5	24	17
2	10	40	27
3	15	51	41
4	30	63	48
5	45	75	72
6	60	87	83
7	90	89	89
8	120	92	89

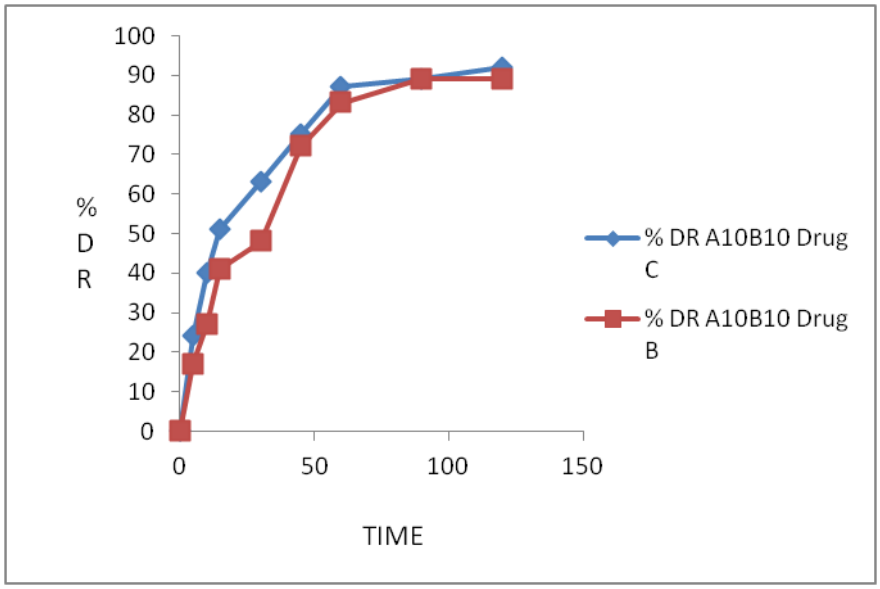


Fig 5.23 Dissolution profile of A10B10 batch

From the above dissolution profile it can be seen that by increasing the disintegration rate the dissolution has been faster and it was concluded 25% disintegrate is optimum to get desired dissolution

Table 5.25 Evaluation parameter of validation batch

Sr. no	Batch no.	Shape	Friability	DT	Size distribution
1	A11	Spherical shaped	0.54%	7 mins 05 sec	0.8- 1.2 mm
2	B11	Spherical shaped	0.56%	7 mins 15 sec	0.8- 1.2 mm

From above result it can be concluded that all parameter are within specified limit.

Table 5.30 Dissolution profile of A11B11 batch

Sr.no	Time (min)	% Drug release	
		A11B11	
		Drug C	Drug B
1	5	26	19
2	10	43	29
3	15	54	43
4	30	67	48
5	45	78	74
6	60	89	83
7	90	92	89
8	120	92	90

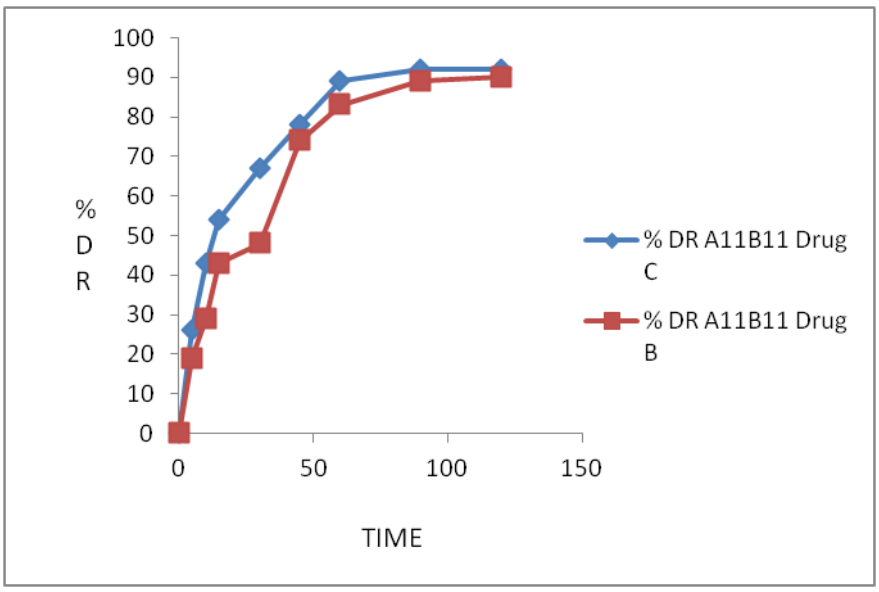


Fig 5.24 Dissolution profile of A11B11 batch

From all the above result it was concluded that batch AB 11 was found out to be most satisfactory batch and was further kept for stability study.

5.9 Container closer system for pellets

Selection of Packaging material

Pellets filled in capsule were kept in white opaque HDPE 60 CC Bottles with CRC cap & induction sealing was done along with absorbent cotton.

Justification: White opaque HDPE bottles provide complete protection against light, water vapor, gases etc.

5.10 Stability study for pellets

Condition: Batch A11B11 at 40°C ± 2°C / 75% RH ± 5 % RH

Packaging: white opaque HDPE 60 CC Bottles with CRC cap & induction sealing was done along with absorbent cotton.

Table 5.31 stability study of pellets

S R. NO	PARA-METER	TI-ME	INTIAL		1 MONTH		3 MONTH	
			DR A	DR B	DR A	DR. B	DR A	DR. B
1	ASSAY	---	98 %	99.53 %	97.93 %	99.12 %	97 %	98.87 %
2	DISSO. MEDIA 1000 ml 6.8 phospha te buffer 75 RPM	5	40 %	38 %	45 %	32 %	35 %	38 %
		10	54 %	56 %	52 %	48 %	58 %	51 %
		15	61 %	67 %	68 %	72 %	64 %	69 %
		30	99 %	83 %	96 %	81 %	97 %	81 %
		45	99 %	89 %	96 %	87 %	98%	86 %
		60	98 %	94 %	97 %	91 %	98 %	90 %
3	DT	--	7 min 04 sec		1min 14 sec		1min 18 sec	
4	FRIABITY	--	0.48%		0.50%		0.50%	

Discussion:

There is no change in description of tablet after 3 month stability study, it reveals that the product is stable at 40°C ± 2°C / 75% RH ± 5 % RH for 12 Weeks (3 months)

Discussion

- From all the experimental work done about it was seen the IR tablets formulated showed similar dissolution profile as compared to that of innovated and was found to be stable throughout the process of stability study.
- The other approach used was pelletization but it was seen from the result that in pellets the release of medicament as fast as it was in tablet formulation, which is a desired criteria for immediate release formulation.
- But in pellets flow properties and dose dumping can be avoided
- Thus both the formulation have its own advantages and disadvantages
- But compared to pellets, tablets can be more preferred one for immediate release formulation.

SUMMARY AND CONCLUSION

SUMMARY:

- The aim of dissertation entitled "Formulation development & evaluation of immediate release dosage form of anti-hypertensive drug in combination" was to develop a stable formulation of tablet and pellets.
- Tablets were prepared Wet granulation method by using water as binding agent.
- The problem of sticking and capping occurred during the formulation of batches due to some unknown problem in quality of sodium steryl fumarate.
- This was resolved by changing the vendor source of sodium sterly fumarate.
- The among all trail batches F7 was found to be most satisfactory batch and it was kept for stability study and not change in stability was found after 3 months.
- Secondly formulation of pellet by extruder spheronizer was done and effect of speed, solvent and disintegrate was studied.
- AB 11 was found to be most satisfactory batch and was kept for stability study and was found to be stable during 3 months of study.

CONCLUSION:

- From all the above work it can be concluded that for the treatment of hypertension fix dose combination can improved patient compliance as well can also improve the therapeutic efficacy of drug.
- Immediate release formulation such as tablet dosage form can be con be consider as one of the best way to administered as fix dose combinations.
- From all the experimental work done about it was seen the IR tablets are the most suitable approach to delivery of agent like anti hypertensive drug, where they are the most wide used technique they also come with their own limitation like poor flow property of blend ,sticking , capping and dose dumping effects.
- To overcome such issue pelletization technique can be utilized it offer various advantages over tablets s it is a multi- particulate drug delivery system.
- But generally pellets are more preferred for extended release formulation, but they can be used for IR release formulation.

REFERENCES

[1] Ravichandiran, V., Patil Vishal, S., & Shanmugarajan, T. S. (2015). International Research Journal of Pharmacy, *4*(2), 20–24.

[2] Gradman, A. H., Basile, J. N., Carter, B. L., & Bakris, G. L. (2010). Combination therapy in hypertension. *Journal of the American Society of Hypertension*, *4*(1), 42–50. https://doi.org/10.1016/j.jash.2010.02.005

[3] Sica, D. A. (2004). Fixed-dose combination therapy--is it time for this approach to hypertension and dyslipidemia management? *Journal of Clinical Hypertension (Greenwich, Conn.)*, *6*(4), 164–167. https://doi.org/10.1111/j.1524-6175.2004.02874.x

[4] Nandhini, S. (2014). Essential hypertension –A review article. *Journal of Pharmaceutical Sciences and Research*, *6*(9), 305–307. https://doi.org/10.1056/NEJM199807233390404.

[5] Arora, A., Shafiq, N., Jain, S., Khuller, G. K., Sharma, S., & Malhotra, S. (2015). Development of sustained release "NanoFDC (Fixed Dose Combination)" for hypertension - An experimental study. *PLoS ONE*, *10*(6), 1–13. https://doi.org/10.1371/journal.pone.0128208

[6] Haritha, B. (2017). Formulation Science & Bioavailability, *1*(1), 1–5.

[7] Neeraj, B., Abhishek, K., Abhilash, C., Rubia, C., & Rajni, B. (2014). a Review on Immediate Release Drug Delivery System. *Int. Res J Pharm. App Sci. International Research Journal of Pharmaceutical and Applied Sciences (IRJPAS) Www.Irjpas.Com Int. Res J Pharm. App Sci*, *4*(41), 78–8778.

[8] Administration, U.S. Department of Health and Human Services Food and Drug (CDER), C. for D. E. and R. (2015). Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs Guidance for Industry Dissolution Testing and Specification Criteria for Immediate-Release S. *Food and Drug Administration*, (August), 5.

[9] Manish Jaimini, Ranga, S., Kumar, A., Sharma, S. K., & Chauhan, B. S. (2013). A Review On Immediate Release Drug Delivery System. *Journal of Drug Discovery and Therapeutics*, *1*(12), 21–27.

[10] Tract, A. B. S. (2012). J ournal of S cientific R esearch in P harmacy, *1*(2), 20–26.

[11] Noyal sundeep, M. G. (2013). Review Article Immediate Drug Release Dosage Form : a Review. *Journal of Drug Delivery & Therapeutics*, *3*(2), 155–161. https://doi.org/10.22270/jddt.v3i2.457

[12] Rathod, V. G., Kadam, V., Jadhav, S. B., & Bharkad, V. B. (2014). Immediate release drug delivery system: a review. *World Journal of Pharmacy and Pharmaceutical Sciences*, *3*(6), 545–558.

[13] Jaimini, M., & Rawat, S. (2013). A review on immediate release drug delivery system. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, *4*(2), 1721–1730.Iii, U. (2012). Unit iii. *Read*, 23–25.

[14] Tousey, M. (2015). The Manufacturing Process: Tablet and Capsule Manufacturing. *Time*, *15*, 1–12.

[15] Sirisha, V. R. K., Sri, K. V., Suresh, K., Reddy, G. K., Devanna, N., Pradesh, A., … Pradesh, A. (2013). a Review of Pellets and Pelletization Process - a Multiparticulate Drug Delivery System. *International Journal of Pharmaceutical Sciences and Research*, *4*(6), 2145–2158. https://doi.org/10.13040/IJPSR.0975-8232.4(6).2145-58

[16] Factor, I., Gupta, A. M., Shivhare, U. D., & Suruse, P. B. (2015). International Journal of Pharmaceutical and Different Aspects of Pellets Formulation and their Evaluation, *4*(6), 331–336.

[17] Ahir, A. A., Mali, S. S., Hajare, A. A., Bhagwat, D. A., & Patrekar, P. V. (2015). Pelletization technology: Methods and applications - A review. *Research Journal of Pharmacy and Technology*, *8*(2), 131–138. https://doi.org/10.5958/0974-360X.2015.00023.2

[18] Singh, S. K., Singh, S., Seth, N. R., Ushir, Y. V., Patel, R., & Singh, A. (2009). Design, development and evaluation of domperidone pellets. *International Journal of PharmTech Research*, *1*(3), 885–891.

[19]Muley, S., Nandgude, T., & Poddar, S. (2016). Extrusion–spheronization a promising pelletization technique: In-depth review. *Asian Journal of Pharmaceutical Sciences*, *11*(6), 684–699. https://doi.org/10.1016/j.ajps.2016.08.001

[20] Sinha, V. R., Agrawal, M. K., Agarwal, A., Singh, G., & Ghai, D. (2009). Extrusion-Spheronization: Process Variables and Characterization. *Critical Reviews™ in Therapeutic Drug Carrier Systems*, *26*(3), 275–331. https://doi.org/10.1615/CritRevTherDrugCarrierSyst.v26.i3.20

[21] Chaudhari, P., Sonawane, R., & Deore, P. (2017). Pelletization techniques : Novel approach for drug delivery, *6*(2), 3–10.

[22] Bathool, A., Vishakante, G. D., Khan, M. S., & Gupta, V. K. (2011). Pelletization as a key tool for oral drug delivery : A review. *Journal of Phamacy Research*, *4*(10), 3282–3286.

[23] Veena, M., Senthil Kumar, S., & Parthiban, S. (2012). Pelletization technique in drug delivery system- A review. *International Journal of Pharmaceutical Development & Technology*, *3*(1), 13–22.

[24] Sirisha, V. R. K., Suresh, K., Vijayasree, K., Devanna, N., & Murthy, P. N. (2014). Recent advances in pelletization techniques - A review. *International Journal of Pharmaceutical Sciences Review and Research*, *27*(1), 217–223.

[25] Zaman, M., Saeed-Ul-Hassan, S., Sarfraz, R. M., Batool, N., Qureshi, M. J., Akram, M. A., … Danish, Z. (2016). Pellets and pelletization: Emerging trends in the pharma industry. *Acta Poloniae Pharmaceutica - Drug Research*, *73*(6), 1415–1425.

[26] Yadav, N., & Verma, A. (2016). Pharmaceutical pellets: A versatile carrier for oral controlled delivery of drugs. *Indian Journal of Pharmaceutical Education and Research*, *50*(3), S146–S160. https://doi.org/10.5530/ijper.50.3.27

[27] Debjit Bhowmik, S.Duraivel, R. A. . and K. P. S. K. (2014). Tablet manufacturing processs and defects of tablets (PDF Download Available). *Elixir International Journal*, *70*(May 2014), 24368–24374. Retrieved from https://www.researchgate.net/publication/277014530_Tablet_manufacturing_processs_and_defects_of_tablets

[28] Rajasree, P. H., Vishwanad, V., Cherian, M., Eldhose, J., & Singh, R. (2012). I NTERNATIONAL J OURNAL OF P HARMACY & L IFE S CIENCES Formulation and evaluation of antiseptic polyherbal ointment, *3*(10), 2021–2031.

[29] Kumari, B., & Garg, R. (2015). World Journal of Pharmaceutical Sciences Drug Profile of Valsartan : A Review.

[30] Brahmaiah, B., Sasikanth, K., Nama, S., Khan, P. A., & Pradesh, A. (2013). Formulation and Dissolution Study of Valsartan Immediate Release Tablets. *Indian Journal of Pharmaceutical & Biological Research (Ijpbr)*, *1*(2), 1–8.

[31] Kumar, S., Gupta, P., & Dev, R. (2013). Formulation and Evaluation of Immediate Release Tablet of Telmisartan, *1*(3), 215–223.

[32] Siraj, S., Khan, G. J., Huzaifa, P., Mohsin, S., & Sufiyan, W. (2015). International Journal of Innovative Pharmaceutical Sciences and Research. *International Journal of Innovative Pharmaceutical Sciences and Research*, *3*(1609), 1609–1625. https://doi.org/10.13040/IJPSR.0975-8232.5(5).1914-18

[33] Jagdish, N., Mahesh, J., Viren, a, Vrajesh, K., Compounds, B. H., & When, A. (2008). Saurashtra University.

[34] Gandhi, B., & Baheti, J. (2013). Multiparticulates Drug Delivery Systems : A Review. *International Journal of Pharmaceutical and Chemical Sciences*, *2*(3), 1620–1626.

[35] Nadeem, S., Asif, H., Lakshita, C., M Shamsher, A., Moloy, M., & Parminder, S. B. (2011). Pharmacological and Pharmaceutical Profile of Valsartan: A Review. *Journal of Applied Pharmaceutical Science*, *01*(04), 12–19.

[36] Lakshmi, P. K., Srinivas, C., & Kalpana, B. (2011). Preparation and comparative evaluation of liquisolid compacts and solid dispersions of Valsartan. *Stamford Journal of Pharmaceutical Sciences*, *4*(2), 48–57. https://doi.org/10.3329/sjps.v4i2.10440

[37] Redasani, V. K., Patel, P. V, & Surana, S. J. (2011). Spectrophotometric method for simultaneous estimation of Valsartan and Hydrochlorothiazide in combined tablet dosage form. *Der Pharmacia Sinica*, *2*(3), 123–130.

[38] Pande, V., Karale P, Goje P, & Mahanavar S. (2016). An Overview on Emerging Trends in Immediate Release Tablet Technologies. *Austin Therapeutics*, *3*(1), 1026.

[39] Gupta, K. R., Wadodkar, A. R., & Wadodkar, S. G. (2010). UV-spectrophotometric methods for estimation of valsartan in bulk and tablet dosage form. *International Journal of ChemTech Research*, *2*(2), 985–989.

[40]Jogad, N. P., Bhairy, S., Nostrum, E., Pvt, R., … Zhang, X. (2012). Tablets Manufacturing Methods and Granulation Techniques. *Ijpsr*, *3*(3), 1793–1797. https://doi.org/10.1016/j.ajps.2013.12.005

[41]https://www.researchgate.net/Handbook-of-pharmaceutical-excipients-6th-edition.pdf

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