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Formulation, Optimization And Evaluation Of Linagliptin Immediate Release Tablet

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Abstract:-

Tablets are a popular dosage form due to their convenience, compactness, and ease of manufacturing. Immediate release tablets, which dissolve quickly in the stomach, are particularly useful when the action required. Immediate release tablets dissolve quickly in the action required.Immediate release tablets dissolve quickly in the stomach and are especially useful when quickly start is needed Superdisintegrants such as croscarmellose and sodium starch glycolate are frequently used in the tablet formulations to improve drug dissolutions and promote immediate disintegration.The tablets now available and promote immediate disintegration.The tablets now available have good patient compliance and are suitable for many types of medications.They also provide opportunities for business growth.

This review provides detailed information about the mechanism of action, preparation pr ocess, excipients and evaluation of readymade tablets. In general, now released tablets ar e becoming more popular than dispensing machines.

Keywords.:- *Immediate release, Disintegration, Superdisintegrant*

INTRODUCTION:

Drug Delivary System: [1,4,8,22,24,25]

The oral administration method is the most popular mode of operation because it is easy to take, avoids pain, avoids many things, and most importantly, patient compliance. Additionally, since oral devices do not need to be sterile, they are cheaper to produce. Tablets are the preferred dosage form due to patient compliance, high precision dosing, and production efficiency.The oral route is still the best route for medical use due to the low cost of treatment, low production costs, and easy administration. and gastrointestinal mucosa. In particular, digestion time may vary between patients and within the same patient; Time in the stomach is the most variable depending on the level of dosage form and the fasting or eating status of the patient.The pH in the intestine also varies ,from the low pH in the stomach (1.5-2 in the fastest state to about 5 in the fed state) to the higher pH in the small and large intestines.

Table No.1 : Lists the pH ranges in the GIT

Region	Surface area (m^2)	pH of the region	Transit time Of fluid	Transit time Of Solid
GIT	200	-	-	-
Stomach	0.1-0.2	1.3-5	50 min	8 hours
Small intestine	4500	5-7.5	2-6 hours	4-9 hours
Large intestine	0.5-0.1	6.8	2-6 hours	3 hours to 3 days

Tablet :

A compressed solid dosage form containing medicaments with or without excipients is known as tablet.There are the most popular form of medication available today due to their ease of administration ,compactness and ease of manufacture .however,in most cases ,emergency treatment is not a routine treatment. Tablets are the most used form due to their unique features as ease of a administration ,low cost,and non-invasive treatment.The effectiveness of any treatment depends on the patient’s compliance with the treatment. Once the patent expires, pharmaceutical companies often develop new and improved versions of the drug. Tablet is one

of the products that can be taken orally. Tablets are medication dosage forms that may or may not contain additives.

General Properties Of Tablet :

1. A tablet should have elegant product identity while free of defects like chips, cracks, discoloration & Contamination
2. Should have sufficient strength to withstand mechanical shock during its production packaging,shipping & Dispensing.
3. Should have the chemical and physical stability to maintain its physical attributes Overtime.
4. The tablet must be able to release medicinal agents in a predictable & reproducible manner.
5. Must have a chemical stability over time so as not to follow alteration of the medicinal a gents.

Types And Class of Tablets : [4,18,24]

A. Oral Tablets for Ingestion

1. Compressed Tablets
2. Multiple Compressed Tablets
3. Layered Tablets
4. Compression-Coated Tablets
5. Repeat Action Tablets
6. Delayed-Action & Enteric-Coated Tablets
7. Sugar & Chocolated Coated Tablets
8. Film Coated Tablets
9. Chewable Tablets

B. Tablets used in the oral cavity

1. Buccal Tablets
2. Sublingual Tablets
3. Troches & Lozenges
4. Dental Cones

C. Tablets administered by other routes

1. Implantation Tablets
2. Vaginal Tablets

D. Tablets used to prepare solutions

1. Effervasent Tablets
2. Hypodermic Tablets
3. Tablet Trichurates
4. Dispensing Tablets

Method Of Tablet Preparation :

1. Tablet Moulding Techinque
2. Direct Compression Techinque
3. Granulation Technique
4. Mass Extrusion Technique

Depending on the additional ingredients, an appropriate method is selected for tablet for mulation that will provide the desired properties such as appearance, hardness, disintegration and weight uniformity. Since they are said to be inert in nature, the effect of the product on the stability and bioavailability of the active ingredient as well as on the treatment of the drug should be investigated. The special powder mixture is compressed into tablets using direct compression machines.

Direct Compression Methods :

In this way, the drug and excipient mixture is administered directly into the tablet without the need for pre-treatment.Compressed mixture must be sufficiently liquid and coalesce under pressure, so wet granulation is not necessary. A few drugs can go into tablets that a re directly acting. The type and proportions of the shredder are important. Particle size dis tribution, contact angle, pore size distribution, tablet hardness and water absorption are al so important factors to consider. All of these factors can trigger a breakout. Commercial grade shredder addition technology is both cost-effective and easy to use.

Advantages :

1. Low Labour Input
2. A Dry Process
3. Fewest Processing Steps

Disadvantages:

1. Stratification may occur due to differences in particle size and bulk density which results poorcontent uniformity.
2. Direct compression diluent may interact with the drug. For example, amine drug with Lactose produce discoloration of tablet.

Figure No.1:Direct Compression Processing Steps

Immediate release drug delivary system : [1,2,12,21,24,25,26,28]

The Term immediate release drug formulation refers to a formulation in which the rate of drug release and or absorption from the formulation is not large or is deliberately slowed by galenic manipulation.These are tablets that dissolve and dissolve quickly to the medication. In such cases, if the diluent or carrier does not reduce drug release and/or abs orption, immediate release can be achieved with a suitable diluent or carrier Because this is defined as an immediate release tablet designed to break down and release its drug without special cost management such as special coating and other technologies .Current release tablets are designed to break down and release the drug without the need for cost control such as special coatings or other technologies.immediate release tablets are the most widely used to many types of the medication which are mostly designed to increase ease of administration.The idea of an immediate release drug was born from the desire to provide patient quick effect with different type of medication.The majority of the patients need medications to get quickly results ,which lead to non- compliance with the conventional release Formulation or the tablet treatments and so that therefore, its healing effect decreases.The purpose of immediate delivery is to deliver the therapeutic drug to appropriate place in the body as quickly as possible and then administer the desired drug.Immediate release oral dosage forms are classified as having the rapid or slow dissolution rates.Instant release formulations dissolve 85% of the subscription within the 30 minutes.

Mechanism Of Immediate release dosage form :

The release of the drug from the conventional capsule and its absorption from the gastrointestinal tract depends on two main functions: 1) separation of the tablet into particles and 2) separation of these substances into the blood stream through the intestine.For highly soluble substances, degradation is the rate- limiting step , whereas for poorly soluble substances, dissolution is the rate limiting step Release of drugs from immediate-release tablets.The drug in a layer / layers thin enough to allow rapid penetration of gastric juice, which then allows rapid exudation of the drug. Drugs are placed in a mixture containing support ing materials or other inert materials that dissolve readily in gastric fluid, releasing the drug as a dissolved substances.Use supplements or other material that quickly turn solid when in contact with liquid in the stomach.Both the ingredients and the drug quickly breakdown into liquid.The lake draws water.Drug absorbtion across biological membranes,such as intestinal epithelium is the rate that limits drug transport to the target site.

Drug selection Criteria for Immediate release tablet : [1,2,8,11,15, 17]

1. The IR dosage form should disintegrate or dissolve in the stomach within a short period of time.
2. Be manufactured at a low cost using standard processing and packaging equipment.
3. Be portable with no fragility concerns.
4. Have a pleasant mouth feel.
5. In case of solid dosage,it should dissolve or disintegrate quickly in stomach.
6. It is less sensitive to environmental conditions such as humidity and temperature.
7. Rapid dissolution and absorption of drug,which may result in a rapid onset of action.
8. It should live little or no residue in the mouth after oral administration.

Benefits of immediate release dosage (solid) forms : [8]

1. System of unit doses and long shelf life.
2. It is inexpensive/cost effective.
3. Immediate release improves stability and bioavailability.
4. The maximum amount of drug can be loaded.

5. Useful at lower concentration.
6. Increase patient compliance as a result of rapid drug absorption.

Disadvantages of immediate release dosage (Solid) form: [8]

1. Drugs with a short half-life necessitate frequent dosing.
2. Swallowing issues in peadiatrices & geriatrics.
3. For drugs with a bitter taste,a abd odour,ir are oxygen sensitives,Tablet encapsulation of coating is required to reduce bioavailability issues.
4. The possibility of GI irritation with high concentrations of medications.
5. Drug release at the same time may result in high plasma concentrations,resulting in toxicity.

Bio-Pharmaceutical Considerations: [15,16]

When new drug delivery system put on, it is must those to consider Biopharmaceutical factor like metabolism and excretion.

A.Pharmacokinetics:[26]

Rapid deterioration of drug distribution depends on many factors such as tissue permeabil ity, perfusion rate, drug binding to tissue, disease state, and drug interactions. With this in mind, absorption, distribution, metabolism and excretion are examined. Once absorbed, the drug reaches therapeutic levels and produces pharmacological effects, so the rate of absorption and duration of absorption are important. In large amounts, degradation and therefore biotransformation is delayed. Liver volume is reduced and local blood flow to the liver reduces drug biotransformation through oxidation, reduction, and hydrolysis. A large amount is cleared and excreted by the kidneys as delayed damage, so its effects are slow, thus reducing the half-life of the drug excreted through the kidneys.

B.Pharmacodynamics:[15]

1. Decreased ability of the body to respond reflexive stimuli, cardiac output, and orthostatic hypotension may see in taking antihypertensive like prazosin.
2. Decreased sensitivity of -adrenergic agonist and antagonist.
3. Immunity is less and taken into consideration while administered antibiotics.
4. Altered response to drug therapy-elderly show diminished bronchodilator effect of theophylline shows increased sensitivity to barbiturates.

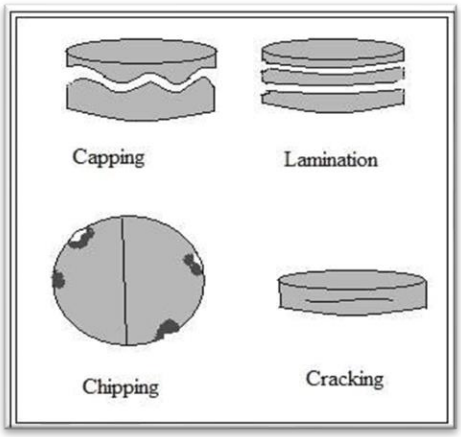
5. Concomitant illnesses are often present in elderly, which is also taken into consideration, while multiple drug therapy prescribed. Research workers have clinically evaluated drug combination for various classes' cardiovascular agents, diuretics, antihypertensive etc. for immediate release dosage forms. The combination choice depends on disease state of the patient.

Problems in tablet manufacturing: [1,12,16,21]

The ideal tablet should have no visual or functional defects. Pharmacists often encounter problems during production. In Most cases, poor visibility is caused by insufficient fines or moisture in the ready to compact mixtures or incorrect adjustment of the machine.

Following are the defects that are found during tablet manufacturing:

1. Weight variation
2. Capping
3. Lamination/Laminating
4. Cracking
5. Chipping
6. Sticking/Picking



7. Mottling
8. Double Impression

Figure No.2:Defects found in tablet manufacturing

General excipients used in immediate release tablets: [5,18,21,27,28]

Idea Characteristics of excipients:

1. They must be non-toxic with no pharmacological activity and acceptable to the regulatory agencies in the countries where the product is to be marketed.
2. They must be commercially available in an acceptable grade in countries where the product is to be manufacture.
3. Cost effective.
4. They must be physiologically inert.
5. They must be physically and chemically stable by themselves and in combination with other drugs and tablet components.
6. They must be free of any unacceptable microbiological load.
7. They must be colour compatible, should not change shade of colour in the formulation.
8. If product is classified as food, the diluents and other excipients must be approved Food additives.
9. They must not have an adverse effect on the bioavailability of the products.

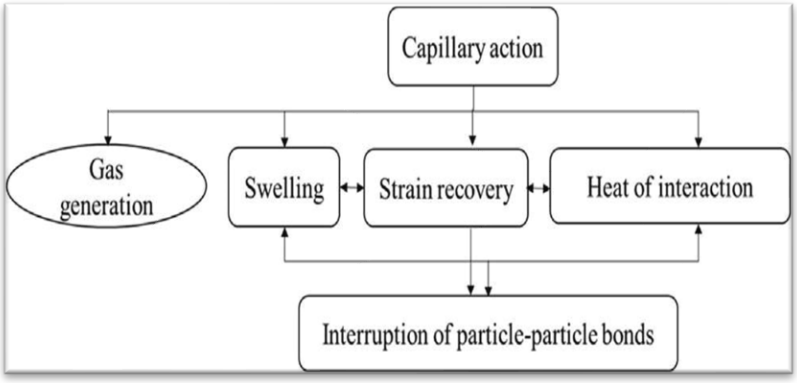
Table No.2 : List of different excipients use in the design of tablets

Excipients	Functions	Examples
Diluents	Used as filler designed to make up the required bulk of the tablet.	Lactose, starch, mannitol, sucrose, sorbitol etc.
Binders and Adhesives	These are used to produce cohesive compact, either in dry or wet form.	Hydroxy propyl methyl cellulose, acacia, starch, cellulose derivative etc.
Disintegrants	Used to facilitate a breakup of the tablet.	Croscarmellose sodium, gellan gum , SSG etc.
Lubricants	Used to reduce the friction during tablet ejection between the walls of die cavity.	Stearic acid, stearic acid salts, PEG, Talc, waxes etc.

Antiadherant	Used to reduce sticking or adhesion of any tablet granules or powder to the faces of punches or die wall.	Talc, PEG, hydrogenated castor oil, glyceryl Behenate etc.
Glident or flow promoters	Used to promote flow of the tablet granules or powder material by reducingfriction within particles.	Silica derivatives, talc,cornstarch etc.
Colours, flavours sweeteners	Used to enhance the Organoleptic properties and acceptability of the product.	FD & C, D&C dyes and lakes, banana, bubble gum, strawberry,vanilla flavours, aspartame, neotame,saccharin, mannitol etc..

Superdisintegrant Agents: **(6,9,15,18,19,20)**

Disintegrants are substances added to tablets and some capsules to promote the disi ntegration of tablets and capsule "chunks" into smaller pieces in an aqueous environ ment, increasing the surface area and promoting faster absorption of the drug. In do sage form, superdegraders are generally used in the low concentrations,usually 1- 10% by weight compared to the total weight of the food Various groups of superdisintegrants such as synthetic ,semisynthetic,natural and coprocessed blends and others are used to improve immediate



release of the tablet and overcome the limitations of the tablet formulations.

Figure No.3 : Schematic representation of relationship between the mechanism of disintegrant action

Mechanism of Disintegration by Superdisintegrants: [6,9,16,19,20]

1. Swelling
2. Porosity and Capillary Action (wicking)
3. Derformation
4. Due to disintegrating particles/particle repulsive forces
5. Enzymatic reaction

1. Swelling : Is believed to be the process by which certain degradants, such as starch, impart their effects. When the tablet comes into contact with water, the adhesion of other compon ents in the tablet is prevented and causes the tablet to break. For e0xample, sodium star ch glycolate.

2. Porosity and Capillary Action (wicking) : It is believed that the good Non-Swelling disintegrant achieves its disintegranting Effect through porosity and capillary action.The porosity of the tablet makes it easier for liquid to penetrate into the tablet.The disintegrating particles themselves(low cohesion and compressibility) makes porosity and put these pathways into into the tablets. Through capillary action, liquid is drawn into these lines or becomes "aggressive", breaking the bonds between the particles and causing the tablet to break For example, crospovidone and croscarmellose.

3. Derformation : The elasticity of starch granules allows them to easily deform under pressure and retu rn to their original position and shape when the pressure is removed. However, when energy is used during tableting, these products are constantly modified and are called "energyrich", referring to the energy they release when they enter water.Due to the disintegrating particles/particle repulsive forces. In according to guyot Hermann’s theory of the particle-particle repulsion water enters the tablet through hydroplilic pores, forming a continuous starch that can transfer water from one to another, having a

significant hydrostatic force. This decomposition mechanism caused by the repulsive forces of the particles must be water.

4. Enzymatic reaction : Enzymes also act as degraders in the body. These enzymes do not bind the linkers and ca use degradation. During expansion, pressure is applied to the outside, causing the tablet to rupture or accelerate water absorption, resulting in various particle volumes and promot ing disintegration.

Material And Methods:

Materials:

Linagliptin (API) was gift sample from Morepen Laboratories Ltd of Baddi , Himachal Pradesh And Excipients such sodium starch glycolate, magnesium stearate, talc, aerosol were Received from maxheal pharmaceutical Pvt. Ltd, And MCC PH 102 from medley pharma Ltd,Gellan Gum from innovative pharma.

Methods:

Tablets were prepared and punched by direct compression method.Immediate release tablet of Linagliptin were formulated by using superdisintegrants like croscarmellose sodium, gellan gum. The composition of immediate release tablet and the total weight of tablet was kept constant 200 mg in all 6 formulations of Linagliptin immediate release tablet.

Procedure for batches prepared using direct compression method.

1. All the ingredients were accurately weighed.
2. All weighed ingredients sifted separately with appropriate sieve/mesh(#60).
3. Linagliptin, MCC, Aerosol and superdisintegrants (GG, CCS) were mixed.
4. Magnesium stearate and talc were added to blend and mixed properly before compression of tablet.
5. above lubricated blend was compressed by using 8mm round punches.

Preformulation Study: [62,66]

Characterization Of Linagliptin:

The characterization of drug was carried out by conducting various physico-chemical tests

including.

Organoleptic Properties:

The drug powder linagliptin was analysed for organoleptic characters such as colour,odour and appearance.

Melting point : [96]

Melting point determination of the obtained drug sample was done because it is a good first indication of purity of sample.Melting point of pure Linagliptin was determined by open capillary method. The capillary was closed at one end and filled with Linagliptin. The tube was placed in digital melting point apparatus. The rise in temperature was noted. The temperature at which the drug melts to a clear liquid and off the apparatus.

Solubility:

A small quantity of drug sample was taken in the test tube and the solubility was dertermined by dissolving the drug in 1 ml of various solvents.

Preparation of Standard Calibration Curve of Linagliptin Using Visible Spectrophotometer

0.1N HCl (pH 1.2): [70]

I.Determination of λ max:

A solution of Linagliptin was prepared in 0.1 N HCl and UV spectrum was recorded using UV visible spectrophotometer. The spectra of Linagliptin in 0.1N HCI scanned in the range of 200-250 nm and A max was observed.

II. Preparation of curve of linagliptin in 0.1 N HCl:

Accurately weighed 10 mg of Linagliptin was transferred to 100 mi volumetric flask and dissolved in 100 ml of 0.1N HCI to obtained concentration 100 ug/ml. Aliquots 0.5, 1, 1.5, 2, 2.5 ml were pipetted out in 10 ml volumetric flask. The volume was made up to the mark with 0.1 N HCl. These dilutions 5,10,15,20, and 25 ug/ml concentration solution of Linagliptin respectively. Absorbance of each solution was measured at 297 nm using UV visible spectrophotometer and 0.1N HCl as r eference standard and the standard curve was generated.

Determination of solubility of linagliptin in water :

Firstly,clean all the apparatus with distilled water, then dried it in hot air oven.In 15 ml of distilled water irbesartan added up to become saturated solution with stirring in the conical flask. After that it put on the magnetic stirrer with hot plate. Then temperature gradually increased at 25°C, 35°C, 45°C, 55°C, 65°C for a hour. From that solution standard and stock solution was

made, then from stock solution 0.5, 1, 1.5, 2, 2.5ml sample was pipetted out taken into 10ml volumetric flask, volume makeup with distilled water and absorbance were taken on UV visible spectrophotometer.

FTIR Spectroscopy : [65,71,72]

Fourier transformed infrared technique was one of the most powerful techniques was identify functional groups. The infrared spectrum of pure Linagliptin, gellan gum, croscarmellose sodium andother excipients was recorded and the spectrum analysis was done. The FTIR spectrum of Linagliptin, gellan gum, croscarmellose sodium & other excipients.

Drug Excipient Interaction study:

The compatibility of the drug and excipients under experimental conditions is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the excipients under experimental conditions not affecting the shelf life of product or any other unwanted effects on the formulations containing the drug The physical mixture of Linagliptin:GG,Linagliptin: CCS & Linagliptin.

DSC Analysis: [71]

DSC is one of the most common analytical techniques used to characterize pharmaceutical solids. This technique is used to study what happens to polymers/ samples upon heating Drug and excipients in the ratio 1:1 was analyzed for DSC.

Characterization of Linagliptin Tablets:

Pre-compression Parameters of Powder Blend:

1.Angle of repose: Angle of repose was measured by using funnel method. The precisely weighed blend was taken in a funnel. The height of the funnel was balanced in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug-excipient blend was permitted to flow through the funnel freely on to the surface. The diameter of the powder cone was determined and angle of repose was calculated using the following equation.

$$\text{Angle of Repose } \theta = \tan^{-1}(h/r)$$

Table No.3 : Relationship Between Angle of Repose and Flowability

Angle of repose	Flowability
25-30	Excellent

31-35	Good
36-40	Fair
41-45	Passable
46-55	Poor
56-65	Very poor
>66	Very, very poor

2.Bulk Density: Bulk density was determined by pouring a weighed quantity of tablet blend into graduated cylinderand measuring the height. Bulk density is the ratio of mass of tablet blend to bulk volume. It was calculated by using following equation.

BD = Mass in gm/Untapped Volume in ml

3.Tapped Density: Accurately weighed amount of tablet blend poured in graduated cylinder and height is measured. Then cylinder was allowed to 100 taps under its own weight onto a hard surface. The tapping was continued until no further change in height was noted. It was calculated by using following equation,

TD = Mass in gm/ Tapped Volume in ml

4.Carr's Index/Compressibility Index: Compressibility is the ability of powder to decrease in volume under pressure using bulk density andtapped density the percentage compressibility of powder was determined. It was calculated by using following equation,

Carr's Index = Tapped Density - Bulk Density/Tapped Density

Evaluation of Immediate release tablet:

Appearance:

The tablets were visually observed for capping, chipping and lamination

Tablet Dimensions/Thickness: [75,76]

The thickness of the tablets was determined by using vernier callipers. Randomly 10 tablets selected were used for determination of thickness that expressed in

Mean ± SD and unit is mm.

Hardness:[66,74]

The hardness of a tablet determines its resistance to shipping, breakage, storage, transportation, handling before use.The hardness of 20 tablets from each formulation was determined using the Monsanto Hardness Tester. The tablet was held in between the tester's two jaws along its oblong axis. At this point, the reading should be zero kg/cm^2. Then constant force was applied by rotating the tablet fractured.

Friability: [65,66,76]

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface during transportation or handling. Roche friabilator was employed for finding the friability of the tablets. For tablets with an average weight of 0.65 g or less take a sample of whole tablets corresponding to about 6.5 g and for tablets with an average weight of more than 0.65 g take a sample of 10 whole tablets. Roche friabilator was rotated at 25 rpm for 4 minutes for 100 rounds. A loss of less than 1% in weight in generally considered acceptable. Percent friability was calculated follows

Percent Friability % F = Initial Weight - Final Weight/ Initial

Weight Variation Test: [74,75]

To determine weight variation, 20 tablets of each formulation were individually weighed using an electronic balance, the average weight was calculated, and the individual tablet weight was then compared to the average value.

Table No.4: Specification for Tablets as Per IP

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

Drug Content: [74]

Ten tablets from each batch were precisely weighed and powdered. The powdered equivalent to 100 mg Linagliptin was weighed and shaken in 100 ml of 0.1 N HCI in a volumetric flask, and 1ml was pipetted out and diluted up to 10 ml. The resulting solution was filtered and measured at 297 nm, and the Linagliptin content was calculated.It was calculated by using formula,

Drug Content = Test Absorbance/Standard Absorbance X 100

Disintegration Time: [65,74]

The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per IP. specifications. It was carried out using an Electrolab disintegration test apparatus. The volume of disintegration medium (distilled water) used was 900ml.1 tablet in each of 6 tubes of basket was placed carefully and add a disc water maintained at 37°c ± 2°c. At the end of time specified basket was lifted from the fluid and observes the tablets. All tablets had disintegrated completely.

Diameter:

Tablet diameter is dependent on the dimensions of the punch tip or punch face so it is critically checked or verified before installation of tooling on the compression machine/other. Example-

Suppose we want to compress a batch of tablets in a round shape having a diameter of 8.0 mm. so for this purpose, we will use round-shaped punches & dies. To produce 8.0 mm round tablets the diameter of punches used should always be 8 mm.

Wetting Time & Water Absorption Ratio: [73,77,78]

The wetting time of the tablet can be measure using a simple procedure. Five circular tissue papers of 10 cm diameter were placed in a Petri dish with a 10 cm diameter. 10 ml of water containing water soluble dye was added to the Petri dish. A Tablet was carefully placed on the surface of tissue paper in the Petri dish at room temperature. The time required for water to reach the upper surface of thetablets and completely wet them was noted as the wetting time. The weight of the tablet before keeping in the Petri dish was noted (Wa). The wetted tablet from the Petri dish was taken and reweighed (Wb). The water absorption ratio, R was determined according to following equation.

Where:

Wb= weight of a tablet after absorption

Wa=weight of a tablet before absorption

$$R = \frac{Wb - Wa}{Wa} \times 100$$

In-vitro Dissolution Studies: [63,64,76]

The USP dissolution test apparatus was used to study the drug release from the tablets. The dissolution medium was 900ml of 0.1 N HCl. The release was performed at 37±0.5°C, with rotation speed 50 rpm. 5ml of sample was withdrawn at pre determined time intervals and replaced with fresh medium. The samples were analyzed after appropriate dilution by UV spectrophotometer 1800 at 297 nm and drug release was determined by following formula,

$$\%\text{Drug Release} = (\text{Test Abs.} / \text{Std. Abs.}) \times \text{Std. Dilution} \times \text{Test Dilution} \times \text{Purity}/$$

Dissolution Parameters:

a. Dissolution machine – Electrolab (TCT-08L)
b. Dissolution apparatus – Paddle type (USP type-II)

c. Product – Linagliptin IRT
d. Dissolution medium – 0.1 N HCL (1.2 pH)
e. RPM – 75 rpm
f. Temperature - 37˚C ± 0.5 ˚C
g. Sampling time – 5, 10, 15, 30, 45, 60 min
h. Wavelength – 297 nm
i. Dissolution medium volume - 900 ml
j. Sample volume withdrawn – 5 ml sample

Dissolution Test of Marketed Formulation:

1. Brand Name : Trajenta 5 mg
2. Strength : Each Uncoated Tablet Contains Linagliptin
3. Colour : Light Red
4. Manufacture by : Boehringer Ingelheim India Pvt Ltd.

Stability Studies:

Stability is defined as the ability of particular drug or dosage for in a specific container to remain within its physical, chemical, therapeutics and toxicological specification. Accelerated stability studies on promising formulation B6 were carried out by storing tablets in bottle at 40°C ± 2°C / 75% ± 5% RHfor 3 months in humidity chamber. At the one month the tablets were examined physical and chemical changes hardness, friability, disintegration time, drug content and in- vitro dissolution study.

Optimization:

Optimization is the process of determining the best way to use existing resources while considering all of the factors that influence decisions in any experiment. The final product not only meets bioavailability requirements, but also practical mass production criteria. Modern optimization techniques based on experimental designs are an essential aid in formulation development because they aid in developing the best possible formulation under a given set of conditions, saving significant time, money, and development effort. Optimization is used for finding a factor combination corresponding to an optimal response profileand robustness testing used as a last test before the release of the product. New formulation developed by using experimental designs in DOE tool. The numerous types of experimental designs are present i.e.,

Central Composite Design, Box-Behnken Design, Factorial Design, Fractional Factorial Design & Optimal Design.

Advantages of Optimization:

- It reduce the cost
- It ensures safety and reduces errors.
- It produce innovation and efficacy
- It saves time.

Parameters of Optimization:

1.Variable types:

a.Independent: The independent variables are under the control of the formulation. These might include the compression force or the die cavity filling or the mixing time.

b.Dependant: The dependent variables are the characteristics that develop in response to the independent variables.

2.Factors : Independent variables will form factors. Variables which can be controlled by an experimenter.

3.Levels : Range of each factor in the study or grade of excipients.

4.Response : Output of the experiment.

Central Composite Design (CCD):

Central composite design (CCD) is a statistical optimization method commonly used in pharmacy and pharmaceutical research. It is a subset of response surface methodology (RSM) and is widely used to study the relationship between multiple variables and their effect on the response or outcome of interest. The Central Composite Design (CCD) was employed to systematically study the experimental designto investigate the effect of three independent variables (factors), i.e., concentration of Gellan Gum (X1), Concentration of Croscarmellose sodium (X2) on the dependant variables, i.e., drug release profile (Y1), disintegration time (Y2).In these study conc. of Gellan Gum (X1), conc. Of Croscarmellose sodium (X2) were considered as formulation variables which varied, as required by experimental design & the number of otherexcipients were kept constant. The drug release profile (Y1), disintegration time (Y2) were selected asresponse variables. All analysis were performed by using the Design Expert Version 13.0.5.0 software.In pharmacy, CCD is used to optimize the formulation of drugs, study

drug release kinetics, and evaluate the effect of various factors on drug stability, bioavailability, and effectiveness. It allows researchers to systematically investigate and optimize the combination and levels of key factors that influence drug characteristics.CCD involves the design and execution of a series of experiments, with different combinations of factors and levels, based on a set of predetermined criteria. The design typically includes both factorial points and axial points. Factorial points represent extreme or minimum/maximum levels of the factors, while axial points help estimate curvature and interaction effects. The response or outcome of interest is measured for each experimental condition.The collected data from CCD experiments are then analyzed using statistical techniques such as regression analysis, analysis of variance (ANOVA), and response surface modeling. These analyses help identify the key factors that significantly affect the response, optimal factor levels for desired outcomes, and any interactions between factors.By utilizing CCD, pharmacy researchers can efficiently optimize drug formulations, identify the critical factors influencing drug properties and develop robust processes for pharmaceutical production.This methodology helps streamline the drug development process, reduce costs, and improve thequality and efficacy of pharmaceutical products.

Applications of Optimization:

- Used in the formulation & processing
- Clinical chemistry
- Medicinal Chemistry
- High performance liquid chromatographic analysis
- Study of pharmacokinetic parameters

Table No.5 : Formulation Variables with Their Actual Coded Values

Independent Variable	**Unit**	**Level**				
		-ᾱ	Low	Medium	High	+ᾱ
GG	%	0.0343	0.2	0.7	7	1.1656
CCS	%	1	1	3	5	1

Table No.6 : Response Variables with Their Actual Coded Values

Response Variable	Actual Coded Values	Unit
% Drug Release	Y1	%
Disintegration Time	Y2	Seconds

Table No.7: Factor Combination as per the Experimental Design

Experiment No.	Gellan Gum (%)		Croscarmellose Sodium (%)	
BLS1	+1	1	-1	1
BLS2	+α	1.16	0	2
BLS3	+1	1	+1	5
BLS4	0	0.6	+α	5.82
BLS5	-α	0.034	0	3
BLS6	0	0.6	0	3
BLS7	0	0.6	-α	0.171
BLS8	-1	0.2	-1	1
BLS9	-1	0.2	+1	5

Table No.8: Formulation Linagliptin IRT Batches by DOE

Sr. No.	Linagliptin	Sodium Starch Glycolate	MCC PH 102	GG	CCS	Mg. Stearate	Talc	Aerosil
B1	05	95	92	2	2	1	2	1
B2	05	95	87.68	2.32	6	1	2	1
B3	05	95	84	2	10	1	2	1
B4	05	95	83.16	1.2	11.64	1	2	1
B5	05	95	89.932	0.068	6	1	2	1
B6	05	95	88.8	1.2	6	1	2	1
B7	05	95	94.45	1.2	0.342	1	2	1
B8	05	95	93.6	0.4	2	1	2	1
B9	05	95	85.6	0.4	10	1	2	1
Avg. Wt.	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

*All ingredients are in mg

RESULT & DISCUSSION:

Characterization of Linagliptin:

A. Organoleptic Properties of Linagliptin:

Table No. 9: Organoleptic Properties of Linagliptin

Sr.no.	Properties	Specification	Observation
1	Colour	A white crystalline powder	A crystalline powder
2	Odour	Odourless	Odourless

3	Taste	Bitter	Bitter

B. Melting Point Determination:

Table No. 10: Melting Point of Linagliptin

Drug (Linagliptin)	Melting point apparatus	DSC (sharp peak)
Standard	197 ˚C - 200 ˚C	197 ˚C - 200 ˚C
Observed	198 ˚C	198 ˚C

C. Solubility:

Table No. 11: Solubility of Linagliptin

Sr. No.	**Media**	**Solubility (gm/ml)**	**Solubility (mg/ml)**
1	1 N NaOH	0.0100	10
2	0.1 N HCl	0.009	9
3	0.01 N HCl	0.004	4
4	0.001 N HCl	0.002	2

Estimation of Linagliptin:

Determination of Linagliptin:

A solution of Linagliptin was prepared in 0.1 N HCl & UV spectrum was recorded using UV visible spectrophotometer. The spectra of Linagliptin in 0.1 N HCL scanned in the range of 200-400 nm & wavelength was observed at 297 nm.

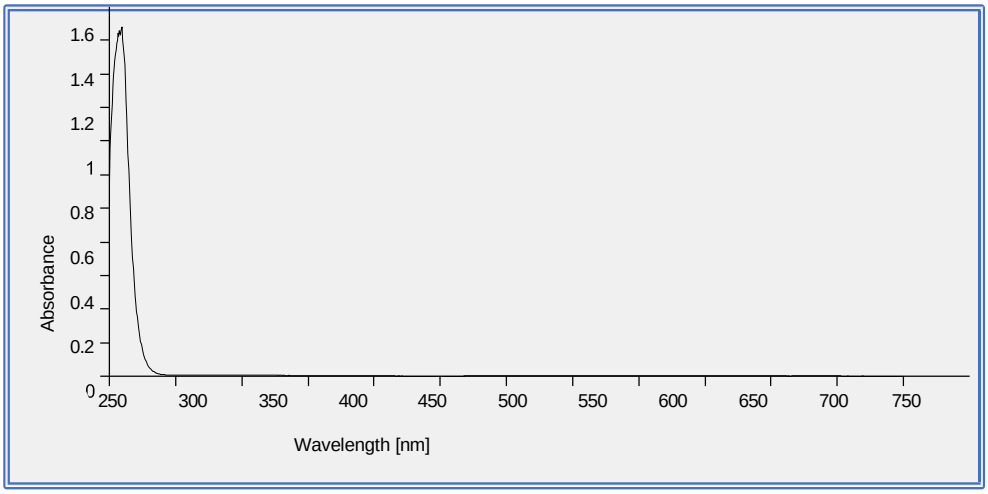


Figure No.4: Determination of Linagliptin in 0.1N HCL

Standard Calibration Curve Of Linagliptin:

Table No.12:Absorbance of Linagliptin

Sr. No.	Concentration (µ/ml)	Absorbance
1	5	0.024
2	10	0.05
3	15	0.075
4	20	0.097
5	25	0.124

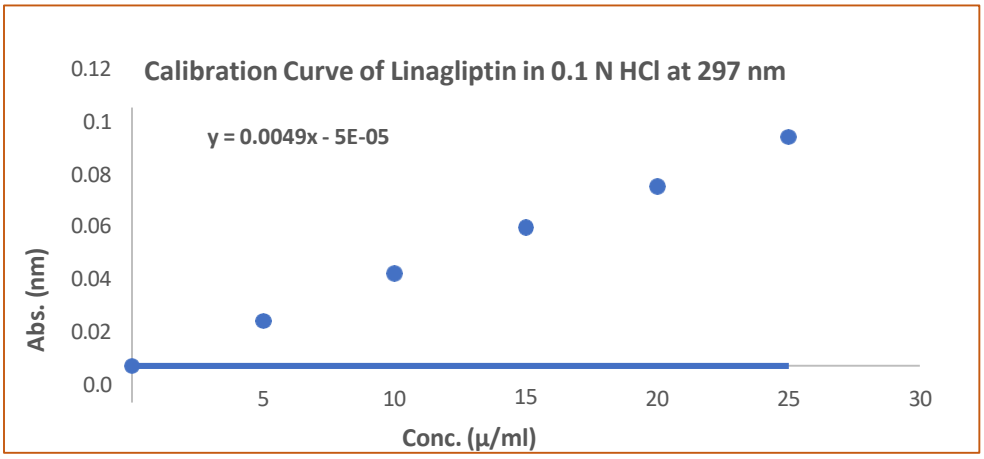


Figure No. 5 : Calibration Curve of Linagliptin

y = 0.0049

R^2 = 0.9995

The standard calibration curve of Linagliptin was obtained by plotting the absorbance of the standard solution against its concentration at 297 nm.

Determination of solubility of Linagliptin in water :

Table No. 13 : Absorbance of Linagliptin in Water

Concentration (µ/ml)	Temperature (˚C)	Absorbance	Solubility
5	25	0.255	0.1679
10	35	0.351	0.3358
15	45	0.479	0.5037
20	55	0.592	0.6717
25	65	0.649	0.8396

Figure 9.3 Solubility Curve of Linagliptin in Water

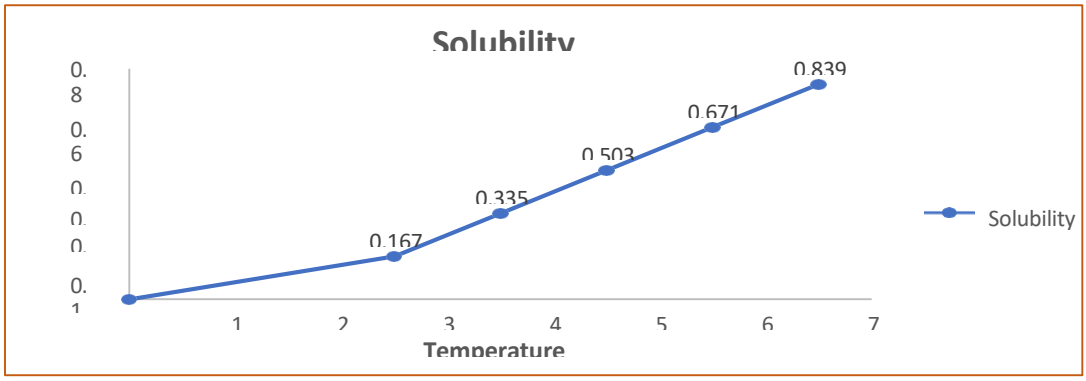


Figure No. 6 : Solubility Curve of Linagliptin in Water

Fourier Transform Infrared Spectroscopy:

A. Linagliptin:

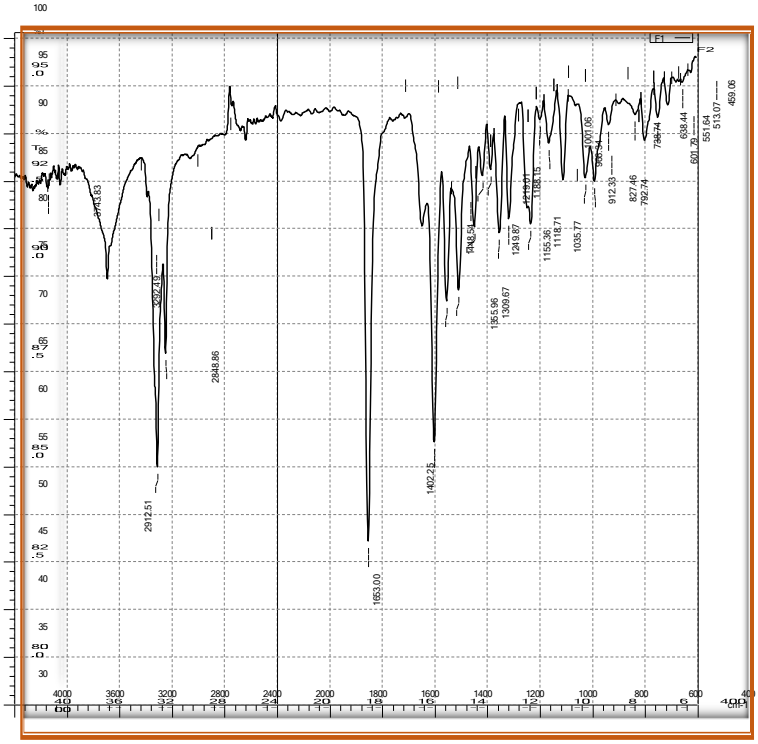


Figure No. 7: FTIR of Linagliptin

Table No.14 : FTIR Interpretation of Linagliptin

Characteristic functional group	**Given Range (cm^{-1})**	**Observed peak (cm^{-1})**
N-H stretching	3500-3100	3292.48
C-H stretching	3000-2850	2812.50
O-H stretching	3400-2400	2848.84
CN	2260-2240	_
C=O stretching	1680-1630	1653.01
CH_2 bending	1465	1448.53

Drug Excipients Compatibility Study:

A. FTIR spectrum of Linagliptin + Gellan Gum

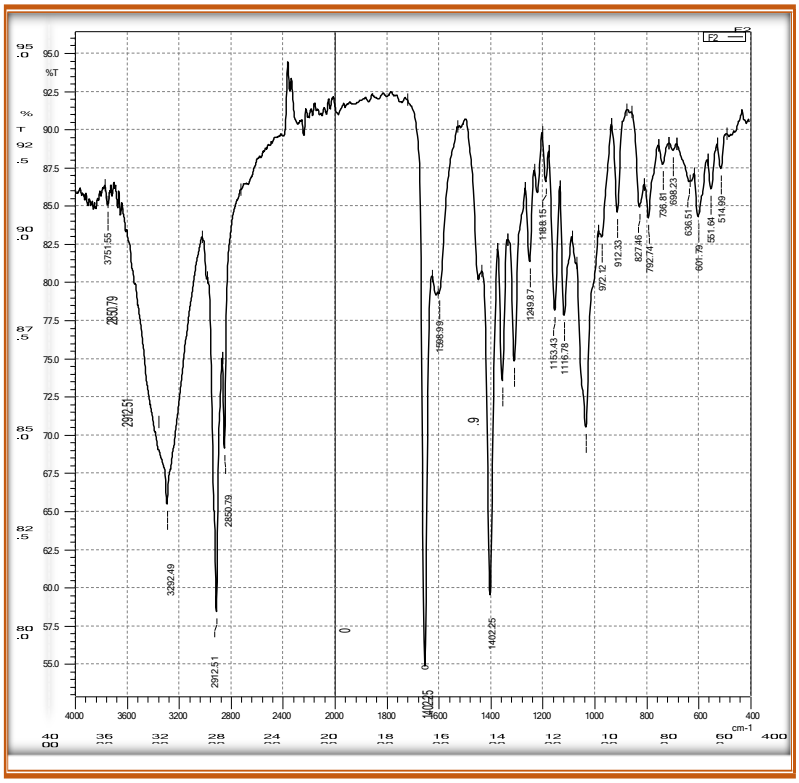


Figure No. 8 : FTIR of Linagliptin with Gellan Gum

Table No. 15 : FTIR Interpretation of Linagliptin with Gellan Gum

Characteristic Functional Group	**Given Range (cm^{-1})**	**Observed Peak (cm^{-1})**
N-H stretching	3500-3100	3292.48
C-H stretching	3000-2850	2812.50
O-H stretching	3400-2400	2848.85
CN	2260-2240	_
C=O stretching	1680-1630	1653.00
CH_2 bending	1465	1448.53
C-O stretching	1085-1050	1033.84

FTIR spectrum of Linagliptin + Croscarmellose Sodium :

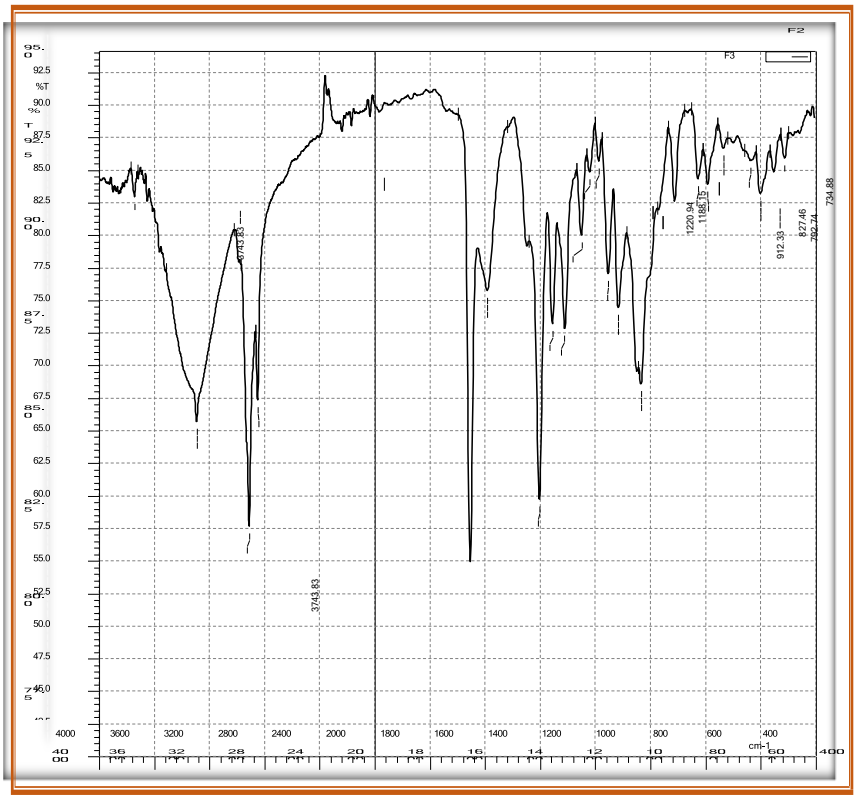


Figure No.9 : FTIR of Linagliptin with CCS

Table No. 16 : FTIR interpretation of Linagliptin with CCS

Characteristic Functional Group	Given Range (cm^{-1})	Observed Peak (cm^{-1})
N-H stretching	3500-3100	3292.48
C-H stretching	3000-2850	2812.50
O-H stretching	3400-2400	2848.85
CN	2260-2240	_
C=O stretching	1680-1630	1653.00
CH_2 bending	1465	1448.53
C-O stretching	1085-1050	1033.84

9.4 FTIR Spectrum of Linagliptin + All Excipients:

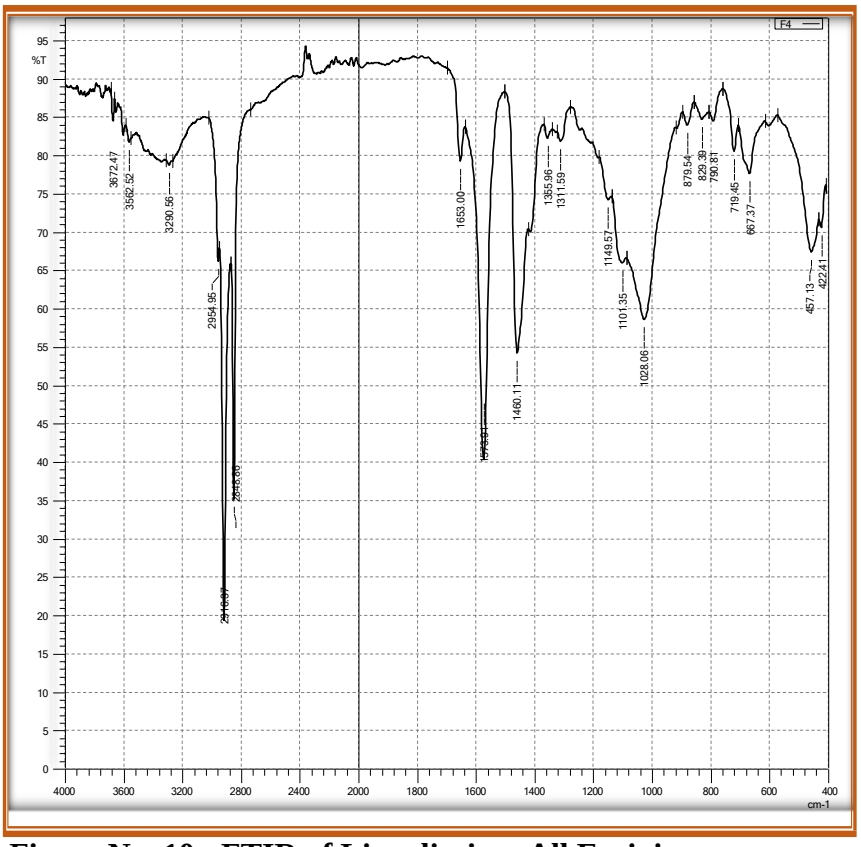


Figure No. 10 : FTIR of Linagliptin + All Excipients

Table.No. 17 : FTIR Interpretation of Linagliptin + All Excipients

Characteristic Functional Group	Given Range (cm^{-1})	Observed Peak (cm^{-1})
N-H stretching	3500-3100	3292.48
O-H stretching	3400-2400	2848.85
C-H stretching	3000-2850	2812.50
CH_2 bending	1465	1448.53
CN	2260-2240	_
C-O stretching	1085-1050	1033.84
C=O stretching	1680-1630	1653.00

Differential Scanning Colorimetry:

The DSC thermogram showed the sharp endothermic peak at 197.22 ˚C represented the melting point of Linagliptin.

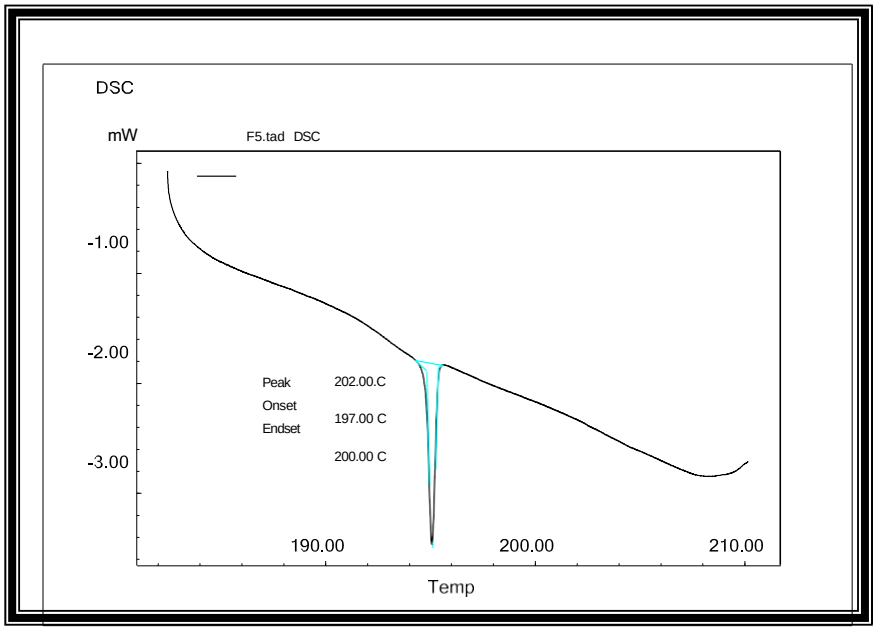


Figure No. 11 : DSC Thermogram of Pure Linagliptin

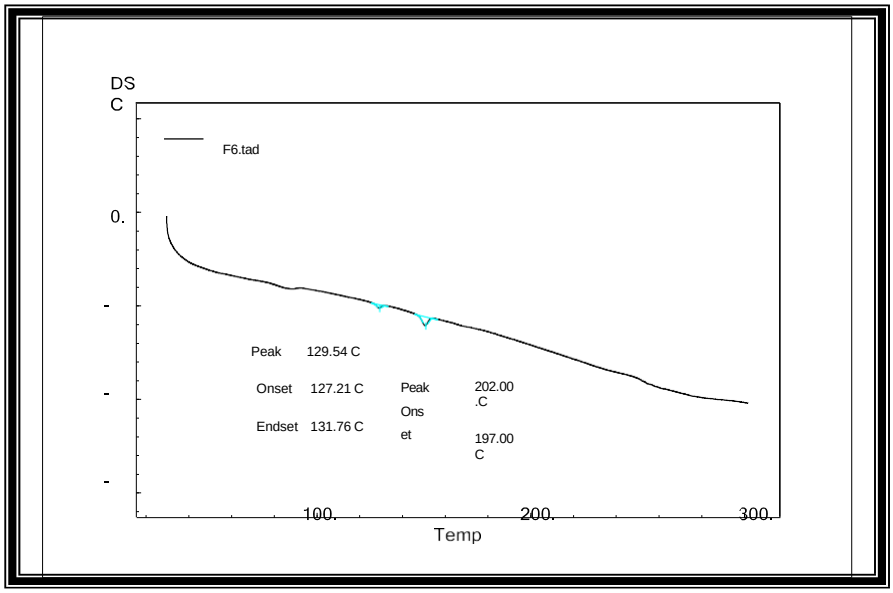


Figure No. 12 : DSC Thermogram of Linagliptin + All blend

The DSC thermogram of Linagliptin & Linagliptin with all excipients shown in fig. 11 & 12

Table no.18 : Thermal Transition & Enthalpy Values of Linagliptin & Linagliptin with All Excipients

Sr. No.	Chemical	DSC Thermal Transition (˚C)	Enthalpy (J/g)
1.	Linagliptin	197 ˚C	−19.76 J/g
2.	Linagliptin + all excipients	197.22 ˚C	−1.15 J/g

Evaluation of Table :

Pre-compression Parameters of Preliminary Trial Batches of Linagliptin Tablet :

Table No.19 : Pre-compression Parameters of Preliminary Trial Batches of Immediate Release Tablets of Linagliptin

Batches	Angle of repose (θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr`s index(%)	Hausner`s ratio
B1	29.5 ±0.022	0.643 ±0.021	0.785±0.010	14.22±1.551	1.22±0.051
B2	26.8 ±0.016	0.658 ±0.011	0.789±0.007	20.15±1.630	1.21±0.021
B3	25.3 ±0.022	0.633 ±0.028	0.792±0.008	14.83±2.719	1.26±0.047
B4	27.5 ±0.014	0.699 ±0.005	0.801±0.011	20.33±1.021	1.28±0.041
B5	26.3 ±0.001	0.687 ±0.001	0.788±0.037	18.217±2.35	1.27±0.049
B6	25.2 ±0.033	0.673 ±0.032	0.781±0.013	17.42±1.105	1.22±0.033

*All pre-compression parameters of preliminary trial batches shown satisfactory results as per their standard limits.

Evaluation of Post-Compression Parameters of Preliminary Trial Batches of Immediate Release Tablets of Linagliptin:

Table No. 20 : Post Compression Parameters of Preliminary Trial Batches of Immediate Release Tablets of Linagliptin

Batches	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)
B1	4.88 ±0.01	3.07 ±0.05	197 ±0.86	0.76±0.012	80.31
B2	4.82±0.003	3.01 ±0.02	199 ±0.02	0.32±0.127	77.95
B3	4.87 ±0.001	3.09 ±0.07	199 ±0.01	0.82±0.061	85.82
B4	4.89 ±0.004	3.07 ±0.05	197 ±0.08	0.72±0.122	102.36
B5	4.88 ±0.003	3.05 ±0.04	196 ±0.08	0.37 ±0.138	92.91
B6	4.86 ±0.002	3.04 ±0.02	198 ±0.08	0.78±0.325	88.97

C. Evaluation of Post-Compression Parameters of Preliminary Trial Batches of Immediate Release Tablets of Linagliptin:

Table No. 21 : Post Compression Parameters of Preliminary Trial Batches of Immediate Release Tablets of Linagliptin

Batches	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)
B1	4.88 ±0.01	3.07 ±0.05	197 ±0.86	0.76±0.012	80.31
B2	4.82±0.003	3.01 ±0.02	199 ±0.02	0.32±0.127	77.95
B3	4.87±0.001	3.09 ±0.07	199 ±0.01	0.82±0.061	85.82
B4	4.89±0.004	3.07 ±0.05	97 ±0.08	0.72±0.122	102.36
B5	4.88±0.003	3.05 ±0.04	196 ±0.08	0.37±0.138	92.91
B6	4.86±0.002	3.04 ±0.02	198 ±0.08	0.78±0.325	88.97

The post compression parameters of preliminary trial batches showed satisfactory results among all batches (B1-B6), batch showed minimum DT i.e.,24 sec.

Table no. 22 : In-Vitro Drug Release of Preliminary Trial Batches of Linagliptin Immediate Release Tablet

Batches	Disintegration Time (sec)	Diameter (mm)	Water absorption ratio (%)	Wetting Time (Sec)
B1	22	8.09 mm	70.55	30
B2	25	8.07 mm	69.84	36
B3	23	8.05 mm	70.85	40
B4	25	8.06 mm	69.19	29
B5	26	8.06 mm	74.48	37
B6	22	8.04 mm	77.00	42

Table No. 23 : % In-Vitro Drug Release

Time (min)	B1	B2	B3	B4	B5	B6
0	00	00	00	00	00	00
5	30.12	22.21	39.82	22.84	39.67	44.39
10	42.19	47.12	52.80	36.11	44.41	59.13
15	53.88	50.84	63.05	47.74	60.12	67.11
30	70.40	75.34	77.12	79.07	76.04	77.98
45	86.90	81.00	84.16	81.06	86.00	80.13
60	94.82	91.47	86.13	85.19	96.41	91.61

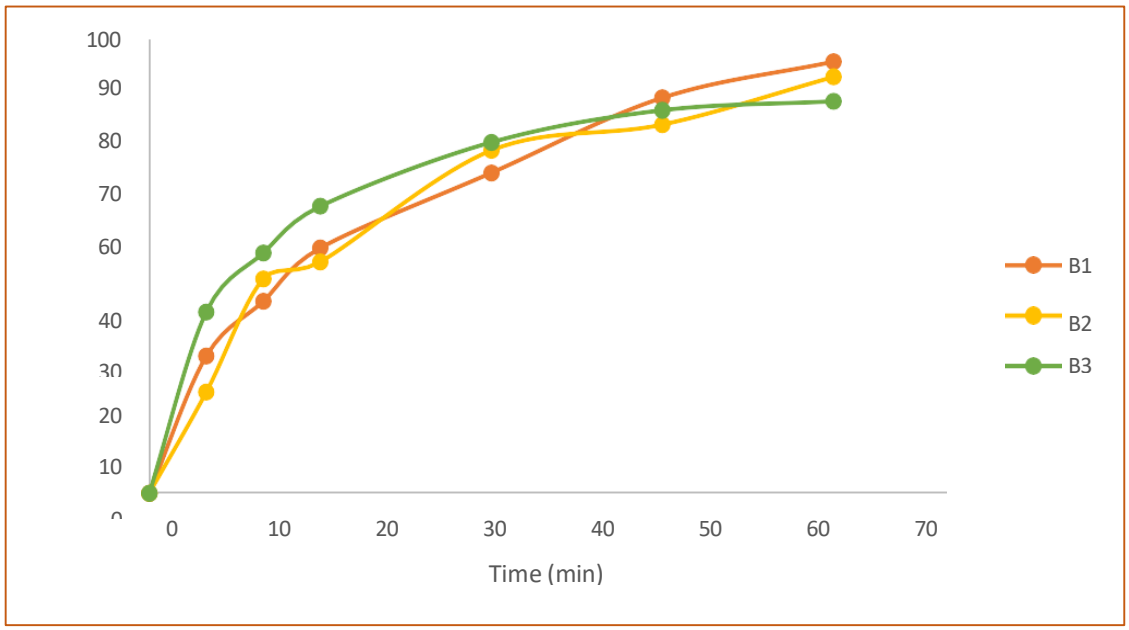


Fig No. 13: In-vitro Drug Release Profile of Preliminary Trial Batches of Immediate Release Tablet of Linagliptin (B1-B3)

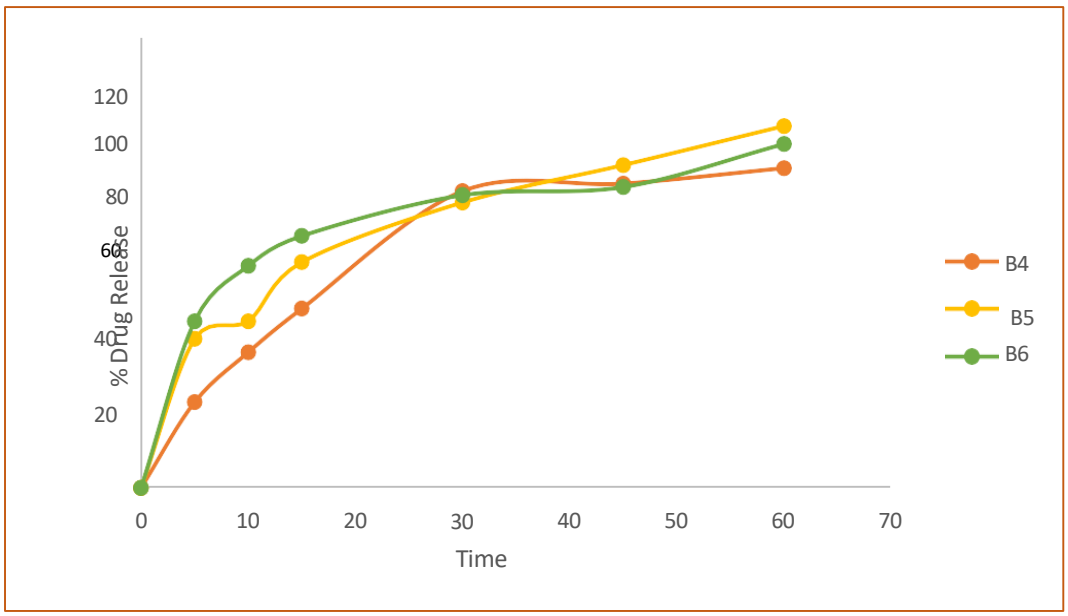


Fig no.14: In-vitro Drug Release Profile of Preliminary Trial Batches of Immediate Release Tablet of Linagliptin (B4-B6)

Evaluation of Batches of IRT of Linagliptin Generated by CCD:

Table No.24 : Pre-Compression Parameter of Batches Generated by CCD

Batches	Bulk density (gm/ml)	Tapped Density (gm/ml)	Compressibility index (%)	Hausner`s ratio	Angle of Repose (θ)
B1	0.42 ±0.03	0.48 ±0.04	12.50 ±0.05	1.14 ±0.03	26.09±0.02
B2	0.39 ±0.07	0.45 ±0.05	13.33 ±0.04	1.15 ±0.02	27.16 ±0.04
B3	0.35 ±0.02	0.41 ±0.03	14.63 ± 0.02	1.17 ±0.04	25.57 ±0.06
B4	0.39 ±0.04	0.50 ±0.04	18.12 ±0.06	1.13 ±0.02	26.38 ±0.05

B5	0.41 ±0.05	0.47 ±0.06	11.11 ±0.03	1.12 ±0.05	28.94 ±0.03
B6	**0.36 ±0.03**	**0.45 ±0.04**	**20.04 ±0.07**	**1.13 ±0.07**	**28.43 ±0.03**
B7	0.38 ±0.02	0.43 ±0.02	10.64 ±0.01	1.13 ±0.03	29.10 ±0.02
B8	0.40 ±0.04	0.45 ±0.05	18.69 ±0.02	1.14 ±0.02	27.64 ±0.04
B9	0.46 ±0.05	0.52 ±0.03	11.54 ±0.03	1.17 ±0.04	25.18 ±0.05

Table No.25 : Post-Compression Parameter of Batches Generated by CCD

Batches	**Hardness (kg/cm^2)**	**Thickness (mm)**	**Weight variation (mg)**	**DT (sec)**	**Wetting time(sec)**
B1	4.55 ± 0.01	4.13 ± 0.01	197 ± 0.86	34.12	36
B2	4.62 ± 0.01	4.11 ± 0.01	197 ± 0.5	26.51	30
B3	4.52 ± 0.01	4.31 ± 0.01	198 ± 0.70	24.1	25
B4	4.6 ± 0.01	4.3 ± 0.01	197 ± 0.70	28.01	30
B5	4.55 ± 0.01	4.19 ± 0.01	197 ± 0.70	28.47	30
B6	**4.55 ± 0.01**	**4.12 ± 0.01**	**197 ± 0.39**	**31.42**	**40**
B7	4.45 ± 0.01	4.13 ± 0.01	197 ± 0.70	36.05	42
B8	4.79 ± 0.01	4.3 ± 0.01	197 ± 0.70	31.08	33
B9	5.13 ± 0.01	4.21 ± 0.01	198 ± 0.70	29.81	32

Table No. 25 : Post-compression Parameter of Batches Generated by CCD

Batches	**Friability (%)**	**Diameter (mm)**	**Water absorption ratio (%)**	**Drug Content (%)**
B1	0.41 ± 0.01	8.09	69.19	93.70 %

B2	0.60 ± 0.01	8.05	70.35	96.06 %
B3	0.7 ± 0.01	8.09	73.36	98.42 %
B4	0.62 ± 0.01	8.08	70.70	100.78 %
B5	0.46 ± 0.01	8.06	73.97	92.91 %
B6	**0.50 ± 0.01**	**8.14**	**85.07**	**98.20 %**
B7	0.63 ± 0.01	8.12	81.09	90.55 %
B8	0.66 ± 0.01	8.07	78.78	88.97 %
B9	0.7 ± 0.01	8.09	72.08	97.63 %

Table No.26: % In-Vitro Drug Release of Batches by DOE Software

Time (min)	**% Drug Release**								
	BL S1	**BL S2**	**BL S3**	**BL S4**	**BL S5**	**BL S6**	**BL S7**	**BL S8**	**BL S9**
0	0	0	0	0	0	**0**	0	0	0
5	31.17	25.50	31.17	42.51	22.67	**34.00**	39.67	22.67	41.09
10	44.63	44.63	58.80	50.30	36.13	**40.38**	45.34	37.55	50.30
15	53.84	61.64	63.05	59.51	41.80	**50.30**	60.22	47.46	58.09
30	72.26	82.89	77.22	78.64	70.13	**77.22**	76.51	74.39	79.35
45	84.31	97.77	97.06	82.18	79.35	**89.98**	77.22	77.22	80.76
60	91.05	103.44	99.60	97.77	90.21	**96.62**	84.31	86.43	94.93

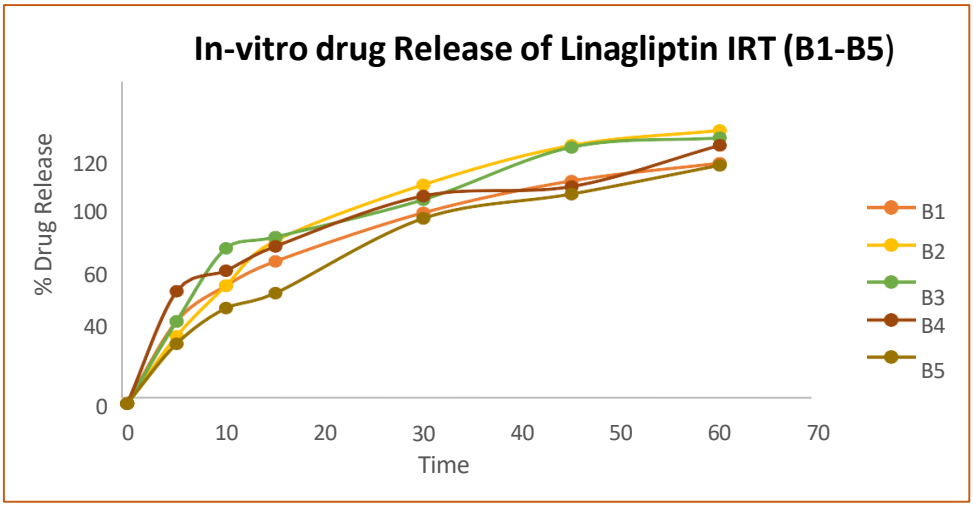


Fig No.15: In-Vitro Drug Released Study of Optimized Batches of Linagliptin IRT Generated by Cental Composite Design (B1-B5)

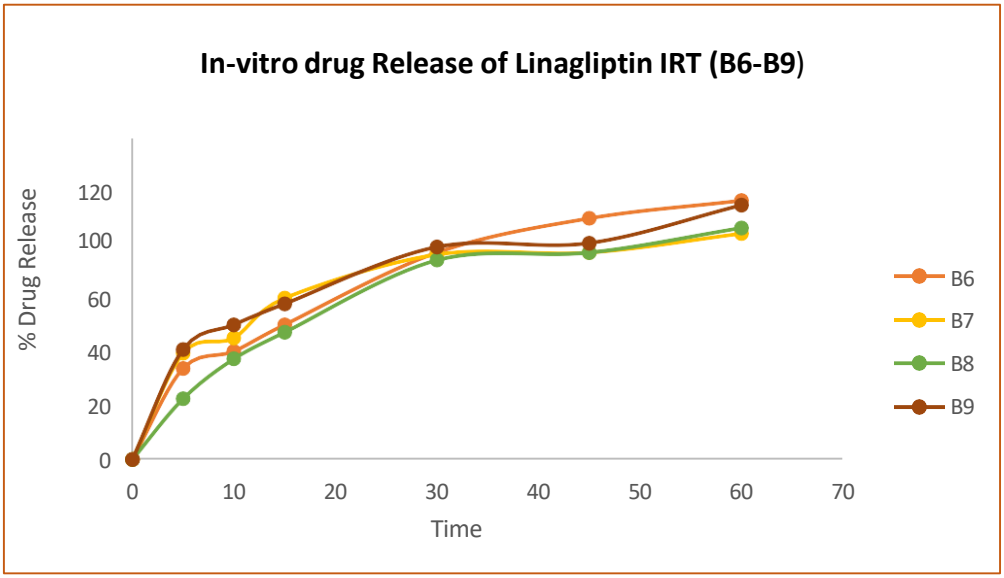


Fig No.16: In-Vitro Drug Released Study of Optimized Batches of Linagliptin IRT Generated by Cental Composite Design B6-B9)

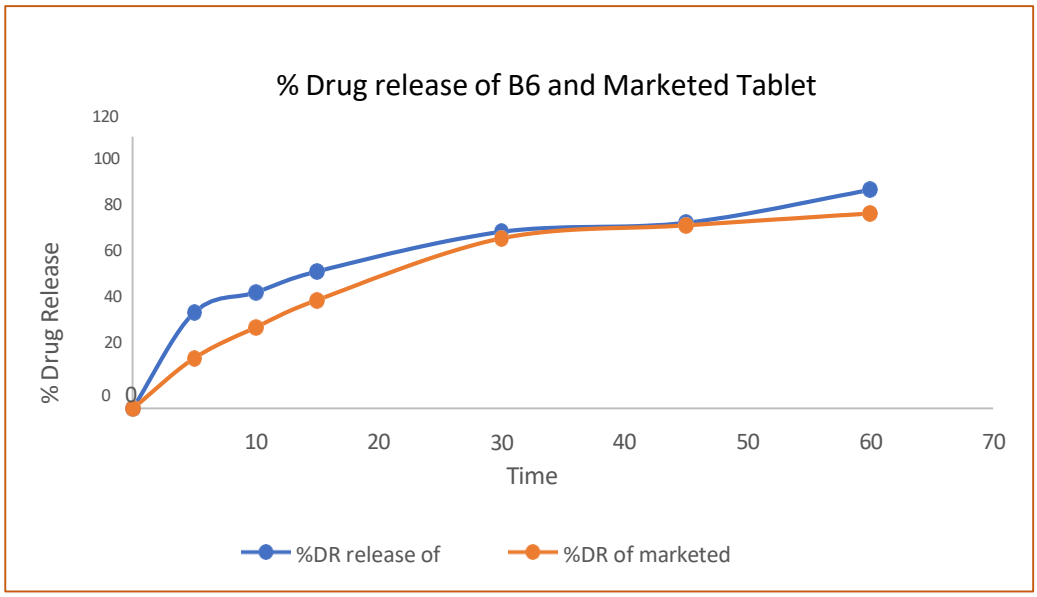


Fig No.17: Comparison of In-Vitro Drug Released of Optimized Batch B6 & Marketed Formulation (Trajenta 5 mg) Uncoated 2 Tablets of Linagliptin.

Optimization and Data Analysis:

Optimization:

Table No.27:Comparison of Percentage Drug Released of Optimized Formulation

Sr. No.	Time (min)	%DR of B6	Time (min)	%DR of Marketed Product
1	00	00	00	00
2	05	42.51	05	22.22
3	10	51.32	10	35.84

4	15	60.63	15	47.91
5	30	78.11	30	75.12
6	45	82.11	45	80.84
7	60	96.62	60	86.12

Stability Study:

A. Accelerated Stability Study

Product Name :- Linagliptin Immediate Release Tablet

Table No.28: Accelerated Stability Data for B6 Optimized Batch of Linagliptin IRT

Parameters		**Condition 40±2^{0}C/75%±5 RH**			
		Initial	**1 Month**	**2 Month**	**3 Month**
Physical	**Average Weight(mg)**	200	199	198	198
	Thickness (mm)	4.0	4.0	4.0	4.1
	Hardness (Kg/Cm^2)	4.10	4.18	4.20	4.20
	Friability (%)	0.52	0.52	0.51	0.50
	DT. Sec.	36	36	37	38

Chemical	**% Drug Release(%)**	99.38	98.84	98.72	98.43
	Drug Content (%)	98.22	99.76	100.46	101.10

B. Long term Stability Study

Product Name:- Linagliptin Immediate Release Tablet

Table No.29: Accelerated Stability Data for B6

Optimized Batch of Linagliptin IRT

Parameters		**Condition 30±2^{0}C/65%±5 RH**			
		Initial	**1 Month**	**2 Month**	**3 Month**
Physical	**Average Weight(mg)**	200	198	198	197
	Thickness (mm)	4.0	4.0	4.0	4.1
	Hardness (Kg/Cm^2)	4.10	4.10	4.10	4.20
	Friability (%)	0.52	0.54	0.54	0.55
	DT. Sec.	36	37	38	38
Chemical	**% Drug Release**	99.39	99.10	98.21	98.67

	Drug Content (%)	98.20	99.78	100.16	101.35

C. Long term Stability Study (Store in Refrigerator)

Product Name: Linagliptin Immediate Release Table

Table No.29: Long Term (Stored in Refrigerator)

Stability Data for B6 Optimized Batch of Linagliptin IRT

Parameters		**Condition 5±3^{0}C**			
		Initial	**1 Month**	**2 Month**	**3 Month**
Physical	**Average Weight (Mg)**	200	199	198	197
	Thickness (mm)	4.0	3.9	3.9	3.8
	Hardness (Kg/Cm^2)	4.10	3.96	3.90	3.90
	Friability (%)	0.50	0.52	0.52	0.53
	DT. Sec.	36	36	35	34
Chemical	**%Drug Release(%)**	99.39	99.02	98.93	98.84
	Drug Content (%)	98.20	98.04	97.98	97.92

Conclusion:

The melting point of the substance was measured with a digital melting poinmt meter and the result was 197^{o}C according to the standard value indicates that the substance is pure. The calibration curve shows a linear relationship between concentration and absorbance. The calibration curve shows a linear relationship between concentration and absorbance. While it follows Beer's Law and Lambert's Law In the range of 5 µg/ml-25 µg/ml. The infrared spectrum is compared to a standard and the peaks of the functional group in the resulting spectrum matches the peak of the functional in the standard infrared spectrum. All significant peaks of the drug were observed in the FTIR spectrum of the mixture and in the DSC study in the melting point peak of the Drug did not change in the mixture. As a result ,the drug and excipient are compatible. First,pre-launch tests were evaluated. All Formulations were found to be satisfactory. All formulations have friability within this range ,i.e.less than 1% . In vitro drug release studies of preoperative experiments were performed using 0.1 N HCL as medium at 75 RPM. Group B6 Showed 99.08% drug release in 30 minutes with a burst time of 20 seconds.Prepare different synthetic superdispersants (gellan gum, croscarmellose sodium) and measure parameters before and after compression. According to the analysis results s pecified in the DOE software, batch B6 was evaluated as the best. All formulations were found to be satisfactory.The friability of batch B6 is 0.50% and all formulations are in the range,i.e.,less than 1% ,0.1 N HCL is used as medium,rotation speed is 75 rpm.Series B6 Drug release on 60 minutes is 96.62% and the disintegration time is 31.42 seconds.The results did not showed any significant change in physical and chemical parameters within 3 months.

References:

1. Rajveer Bhaskar, Monika Ola, Sandip S. Bhamare, A Review on Formulation Approaches in Immediate Release Tablet, **Journal of Drug Delivery & Therapeutics,** 2018; 8(3): 153-161
2. R Mohalkar, B Poul, SS Patil, MA Shetkar, D Chavan; A Review on Immediate Release DrugDelivery Systems, **PharmaTutor,** 2014; 2(8); 95-109
3. Pande V, Karale P, Goje P and Mahanavar S., An Overview on Emerging Trends in ImmediateRelease Tablet Technologies, **Austin Therapeutics**, 2016; 3(1): 1026.
4. Nancy Sharma, Sonia Pahuja and Navidita Sharma, IMMEDIATE RELEASE TABLETS: AREVIEW**, IJPSR** (2019), Volume 10(8), Pg. No. 3607-3618.

5. Jennifer Wang a, Hong Wen b,1, Divyakant Desai, Lubrication in tablet formulations, **European Journal of Pharmaceutics and Biopharmaceutics**, 75 (2010), Pg. No. 1–15.
6. Ashok Dalimbe, Jaydeep Pawar, Shital Bhosale, Nikita Shinde4 , Rushikesh tupe, A Review: Novel Superdisintegrants, **IJCRT,** Volume 9, Issue 7 July 2021, Pg. No. 31-45
7. Abdullah Asiri, Justyna Hofmanova and Hannah Batchelor, A review of in vitro and in vivo methods and their correlations to assess mouthfeel of solid oral dosage forms, **Drug Discovery**, Volume 26, March, 2021, Pg. No. 740-753
8. JISHAN ALI AHMED, A Review on Immediate Release Tablet Dosage Form,

   International Journal of Pharmaceutics, February 2015 Vol.:2, Issue:3, Pg. No. 1-17
9. K.Shobana, L. Subramanian, M. Rajesh, K.Sivaranjani, A Review on Superdisintegrants, **Int. J. Pharm. Sci.**, Vol. 65(2), November - December 2020; Article No. 23, Pages: 149- 154
10. Alberto Berardi, Lorina Bisharat , Julian Quodbach , Safwan Abdel Rahim, Diego R. Perinelli, Marco Cespi, Advancing the understanding of the tablet disintegration phenomenon – An update on recent studies, **International Journal of Pharmaceutics**, 2021
11. Mira Jivraj, Luigi G. Martini and Carol M. Thomson, An overview of the different excipients useful for the direct compression of tablets, **IJPSR,** Vol. 3, February 2000,Pg. No. 58-63
12. Pande V, Karale P, Goje P and Mahanavar S. An Overview on Emerging Trends in ImmediateRelease Tablet Technologies. **Austin Therapeutics**. 2016; 3(1), Pg. No. 1026- 1034
13. Vikas sharma and Vandana arora,COMPARISON OF VARIOUS NATURAL SUPERDISINTEGRANTS IN THE FORMULATION OF FAST DISSOLVING CARDEDILOL TABLET, **IJPSR,** 2012; Vol. 3(10):3947-3954.
14. Md Tausif Alam, Nayyar Parvez, and Pramod Kumar Sharma, FDA-Approved Natural Polymers for Fast Dissolving Tablets, **Hindawi Publishing Corporation Journal of Pharmaceutics**, Volume 2014, Article ID 952970, Pg. No. 1-6

15. Mehulkumar.K.Charan 1,2 , Dr. Alpesh D. Patel1, 2, Dr. Mukesh R. Patel, IMMEDIATE DRUG RELEASE DOSAGE FORM: A REVIEW, **IJPSR,** Volume 4, Issue 3, 2015, Pg. No.614-628
16. Rishikesh, Mohiuddin Ahmed Bhuyian, Ms.Irin Dewan, Drishti Rani Ghosh & Md.Asraful Islam,IMMEDIATE RELEASE DRUG DELIVERY SYSTEM (TABLETS):
    AN OVERVIEW, **Int. Res J Pharm. App Sci.**, 2012, Volume 2,Pg. No.88-94
17. Nancy Sharma , Sonia Pahuja and Navidita Sharma, IMMEDIATE RELEASE TABLETS: A REVIEW , **IJPSR,** 2019; Vol. 10(8), Pg. No.3607-3618
18. Jayesh Parmar & Manish Rane, Tablet Formulation Design and Manufacture: Oral ImmediateRelease Application, **Pharma Times,** Vol 41 - No. 4 - April 2009, Pg. No. 21- 29
19. Parind Mahendrakumar Desai, Celine Valeria Liew, Paul Wan Sia Heng, Review of Disintegrants and the Disintegration Phenomena, **Journal of Pharmaceutical Sciences,** Vol.3, 2016, Pg. No.1
20. P.S Mohanachandran, P.G Sindhumol, T.S Kiran, Superdisintegrants: An Overview, Volume 6,**A Journal of Pharmaceutical Sciences**, Issue 1, January – February 2011, Pg. No.105-10
21. G.moody,M.H. Rubinstein and R.A. Fitz Simmons, Tablet lubricants I- Theory and modes of action**, International Journal of Pharmaceutics**, Volume 9, 1981, Pg. No.75- 80
22. Sharma H. L., Sharma K. K., **Principles of Pharmacology**, 2nd Edition, 2011, Paras Medical Publishers, Hyderabad, Pg. No. 258, 265, 266
23. Dr. S. L. Bodhankar, Dr. N. S. Vyawahare**, Pathophysiology**, 8th Edition, 2012, Nirali prakashan
    Pune, Pg. No. 2.17-2.22
24. Lachman L, Lieberman HA, Schwatz JB, **Pharmaceutical Dosages Forms Tablets**, Volume II, 2ndEdition, Inform Health Care, 1990, Pg. No. 321-330
25. Aulton M. E. , **Pharmaceutics- The Science of Dosage Form Design**, IInd Edition, Churchill Livinstone, Pg. No. 289-305, 489, 491-492
26. Gawarkar PS, Mohite SK, Magdum CS, Adnaik RS, Immediate Release Drug Delivery

System: A review, **IJPSR,** 2015, Vol. 04, Pg. No.576-593

27. Rahul L, Waman, Salunkhe K.S, Chaudhari S. R., Gade A.V., Immediate Release Drug Delivery System: An Overview, **World Journal of Pharmacy & Pharmaceutical Sciences**, 22 Feb. 2016,Vol.5, Pg. No. 2110-2123
28. Dhiman N , Ka,Ini, Kaur M., Pooni N., M. Singh, K Verma, Immediate Release Tablets A Review,**World Journal of Pharmacy and Pharmaceutical Sciences**, Vol. 06, Issue 4, Pg. No. 595-611
29. Oluwafemi Adeleke Ojo, Hannah Sokolayam Ibrahim, Damilare Emmanuel Rotimi, Akingbolabo Daniel Ogunlakin, Adebola Busola Ojo, Diabetes mellitus: From molecular mechanism to pathophysiology and pharmacology, **Medicine in Novel Technology and Devices**, Vol.19, 2023, 100247
30. Harold Edward Bays, why does type 2 diabetes mellitus impair weight reduction in patients with obesity? A review, **Obesity Pillars**, Vol.7, 2023, 100076
31. Natalie Maclean a , Ibrahim Khadra a , James Mann b , Helen Williams c , Alexander Abbott b , Heather Mead c , Daniel Markl, Investigating the role of excipients on the physical stability of directly compressed tablets, **International Journal of Pharmaceutics**, vol.4 (2022), 100106.
32. Karkhile Shubhangi, Kasabe Amit, Barge Vijaya Sakpal Bhavana, Suryawanshi Parija, Formulation and evaluation of a dapsone and fexofenadine HCl immediate release combination tablet, **International Journal of Health Sciences**, 6(S3), Pg. No. 9191–9205.
33. Martin Kalny, Zdenek Grof, Frantisek Stepanek, Microstructure based simulation of the disintegration and dissolution of immediate release pharmaceutical tablets, **Powder Technology** 377 (2021), Pg. No. 257–268.
34. Kunlin Wang, Changquan Calvin Sun, Direct compression tablet formulation of celecoxib enabledwith a pharmaceutical solvate, **International Journal of Pharmaceutics,** 596 (2021), Pg. No. 120239
35. Daniel Markl a,b,* , Natalie Maclean a , James Mann c , Helen Williams d , Alexander Abbott c , Heather Mead d , Ibrahim Khadra, Tablet disintegration performance: Effect of compressionpressure and storage conditions on surface liquid absorption and swelling kinetics, **International Journal of Pharmaceutics**, (2021) Pg. No.120382

36. Fatima Molavi, Hamed Hamishehkar, Ali Nokhodchi, Impact of Tablet Shape on Drug Dissolution Rate Through Immediate Released Tablets, **Advanced Pharmaceutical Bulletin**, 2020, Volume 10,Issue 4, Pg. No. 656-661.
37. Xin Zhang, Jing Zhao, Jian Guan, Xiaofei Zhang, Liang Li, Shirui Mao, Exploration of nanocrystal technology for the preparation of lovastatin immediate and sustained release tablets, **Journal of Drug Delivery Science and Technology,** 50 (2019), Pg. No. 107–112
38. Tanoy Saha, Md. Mahbubul Alam, Dilshad Noor Lira and Abu Shara Shamsur Rouf, Formulation and Evaluation of Effects of Superdisintegrants on Immediate Release Tablet of Linagliptin, a DPP-4 Inhibitor, **Bangladesh Pharmaceutical Journal**, vol. 24(2), 2021 (July), pg. no. 168-179
39. Dalia Gaber1, Siham Abdoun, Hamzah Maswadeh, Ebtihal Alnassr, Maram Al-Salamah, equivalence study of immediate release tablets of beta blocker drug, **Int J App Pharm**, Vol 12, Issue 2, 2020, Pg. No. 53-59
40. Mr. Patel Dhruv, Dr. Patel Upendra, Shukla Maitri, Mr. Bhimani Bhavin, Mr. Patel Ghanshyam,Formulation and Evaluation of Immediate Release Tablet of Simvavstatin, **Research Journal ofPharmacy &Technology**, Vol. 13, 2020, Pg. No. 421-424
41. Reena thakur, Shivali Singla, FORMULATION AND EVALUATION OF IMMEDIATE RELEASE TABLET OF CARVEDILOL WITH NATURAL SUPERDISINTEGRANT AND
    SYNTHETIC DISINTEGRANTS, **Journal of Pharmaceutical Sciences**, 2018, vol. 5(2), Pg. No. 187-194
42. Raina Binu, Shrivastava Birendra, Bhargava Anurag, Sharma Shailesh, Sharma Abhimanyu Rai, Bajwa Prabhjot Singh, Design, development and optimization of immediate release tablet of deflazacort, **Journal of Drug Delivery & Therapeutics**, 2019; 9(2), Pg. No.250-254
43. S. Swati, N. Jyothi, P. Manjusha, N. Lakshmi Prasanthi, B. Thireesha, Formulation and Evaluation of Immediate Release Telmisartan Tablets using Hydrophilic Polymers, **Asian Journal of Pharmaceutics**, Jan-Mar 2018, volume 11, pg. no. 37
44. Garry Scrivens, Prediction of the Long-Term Dissolution Performance of an Immediate-

Release Tablet Using Accelerated Stability Studies, **Journal of Pharmaceutical Sciences,** 2018, Pg. No. 1-10

45. Hanlin Li, David Nadig, Andrew Kuzmission and Christopher M. Riley, Prediction of the changes in drug dissolution from an immediate-release tablet containing two active pharmaceutical ingredients using an accelerated stability assessment program, **Li et al. AAPS Open,** (2016) Pg. No.2-7
46. Swapna Velivela, Vinyas Mayasa, V. Rama Mohan Guptha, Nikunja B. Pati, CH. Ramadevi, formulation, development and evaluation of rosuvastatin calcium immediate release tablets, **European journal of pharmaceutical and medical research**, 2016,3(3), Pg. No. 351-358
47. Netish Kumar Kundo, Sumon Kumar Dutta, Abinash Chandro Sarker, Chand Sultana, Md. Anwarul Haque, Dr. Md. Nurul Islam and Mohammad Mosleh Uddin, Formulation and Evaluation of Rosuvastatin Immediate Release Tablets 10 Mg, **Journal of Pharmacy and Biological Sciences,**Volume 11, Issue 5 Ver. III (Sep. - Oct.2016), Pg. No. 01-05
48. S Madhavi Latha, N Gayatri Devi, N Anusha, M Sameera, N Silpa, N Mehar Lakshmi, Formulation and Comparative Evaluation of Aceclofenac Tablets by Two Granulation Methods, **International Journal of Pharmaceutical and Clinical Research** 2016; 8(7) Pg. No. 649-654
49. Mr. Nirmal H. Shah*, Dr. Hitesh P. Dalvadi, Ms. Pradnya K. Naik, Ms. Archi P. Desai, Ms. Nikita R. Patel, formulation and evaluation of immediate release tablet of cinnarizine and dimenhydrinate,**IJPSR**, vol 7, 04 April 2016, ISSN : 0975-9492
50. Abida Sultana, Fouzia Hassan, Fozia Israr, Syed Muhammad Farid Hasan and Naheed Haque, Formulation and stability evaluation of immediate release antioxidant tablet, **Pak. J. Pharm. Sci**., Vol.27, No.5(Special), September 2014, Pg. No.1393-1400
51. Farghana Begam & N. Rajalakshmi & S. Padmapriya, Formulation and evaluation of thyroid hormone(t3) immediate release tablets, **International Journal of Multidisciplinary Advanced Scientific Research and Innovation**, Pg. No. 383-388.
52. Indian Pharmacopoeia, Government of India, Ministry of Health and Family Welfare, **Indian Pharmacopoeia Commission**, Ghaziabad, Vol-II, India, 2010, Pg. No. 677-678
53. E. B. Polyakova, D. R. Sabirzyanov, N. A. Prozorova, A. V. Footeva, Physicochemical

Properties & Methods of Analysis of Vildagliptin, **Pharmaceutical Chemistry Journal**, Vol. 56, April 2022, Pg. No. 110-117

54. Rowe RC, Paul J Sheskey, Marian E Quinn, Handbook of Pharmaceutical Excipients, Published byThe **Pharmaceutical Press**, Sixth Edition, 2009, Pg. No. 206-208
55. P.V. Prasad, K. Divya, M. V. Ramnava, Analytical Method Development & Validation for The Estimation of Vildagliptin In Bulk And Its Dosage Form Using UV Spectrophotometer, **Indo American Journal of Pharmaceutical Research**, Vol.7, Issue 12, 2017, Pg. No. 1069-1076
56. Tomasz Osmalek, Anna Froelich, Sylwia Tasarek, Application of Gellan Gum in Pharmacy & Medicine, **Ineternational Journal of Pharmaceutics**, 2014, Pg. No. 1-13
57. Md Tausif Alam, Nayyar Parvez, and Pramod Kumar Sharma, FDA-Approved Natural Polymers for Fast Dissolving Tablets, **Hindawi Publishing Corporation Journal of Pharmaceutics**, Volume 2014, Article ID 952970, Pg. No. 1-6
58. Jayesh Parmar & Manish Rane, Tablet Formulation Design and Manufacture: Oral Immediate Release Application, **Pharma Times** - Vol 41 - No. 4 - April 2009, Pg. No. 21-29
59. P.S Mohanachandran, P.G Sindhumol, T.S Kiran, Superdisintegrants: An Overview, **International Journal of Pharmaceutical Sciences Review and Research,** Volume 6, Issue 1, January – February2011, Pg. No.105-109
60. www.Drugbank.com
61. Sunil S. Jambhekar and Philip J. Breen, Drug dissolution: significance of physicochemical properties and physiological conditions, **Drug Discovery Today**, Volume 18, 24 December 2013, Pg. No.73-84
62. Laurence Barthea, John Woodleya, Georges Houina, Gastrointestinal absorption of drugs: methods and studies, **Fundam. Clin. Pharmacol**, Vol. 13, 1999, Pg. No.154-168
63. Mehulkumar.K.Charan, Dr. Alpesh D. Patel, Dr. Mukesh R. Patel, IMMEDIATE DRUG RELEASE DOSAGE FORM: A REVIEW, **World Journal of Pharmaceutical Research**, Volume 4, Issue 3, 2015, Pg. No.614-628
64. Rishikesh, Mohiuddin Ahmed Bhuyian, Ms.Irin Dewan, Drishti Rani Ghosh & Md.Asraful Islam, IMMEDIATE RELEASE DRUG DELIVERY SYSTEM (TABLETS): AN OVERVIEW, **Int.**

Res J Pharm. App. Sci., 2012, Volume 2,Pg. No.88-94

65. Sunil Jain, Mechanical properties of powders for compaction and tableting: an overview, **PSTT,**

    Vol. 2, Issue 1, January 1999, Pg. No.20-31

66. Olutayo Ademola Adeleye, Relationship between compression pressure, mechanical strength and release properties of tablets, **Polymers in Medicine**, 2019, Volume 49 (1), Pg.No.27–33
67. Pande V, Karale P, Goje P and Mahanavar S. An Overview on Emerging Trends in Immediate Release Tablet Technologies, **Austin Therapeutics**, 2016; 3(1): 1026.
68. Anees Ahmed Siddique, Mohmmad Ali, Practical Pharmaceutical Chemistry, Pg. No 77-78
69. D. Dhachinamoorthi, N. Venkateswaramurthy, Biopharmaceutics & Parmacokinetics: APractical Manual, Pg. No. 1-4.7
70. Gary M. Lampman, Donald L. Pavia, George S. Kriz, James R. Vyvyan, 4th Edition, Pg. No. 15- 104
71. Y. R. Sharma, Elementary Organic Spectroscopy, Principles & Chemical Applications, 1st

    Edition, 1980, Pg. No. 69-133

72. The United State of Pharmacopoeia , (USP 30/NF 25), The Official Compendia of
    Standards,**Asian Edition**, 2007, 643
73. Santosh B. Jadhav, Formulation and Evaluation of Immediate Release Tablet of ImipramineHCL,

    IJBAR, Vol.05, 2014, Pg. No. 559-565

74. Lachman L, Liberman HA, Kanig JL, The Theory and Practice of Industrial Pharmacy, 2nd Edition, 2007, **Chuchill Livingstone**, 197-211
75. Indian Pharmacopoeia, 2014,Vol. I, Government of India Ministry of Health and Family Welfare,

Published by The Indian Pharmacopoeia Commission, Ghaziabad, Pg. No. 251-257,960

76. Y. Madhusudan Rao Rao, Kumar YS, Kumar BS, **Advances in Drug Delivery**, Vol. 2, Pg. No. 90-91
77. Chakravarthi KT, prasad AS, reddy RB, formulation & evaluation of levofloxacin immediate release tablets, **IJPRB**, 2015, Vol.4, pg. no. 238-258.