Research on: "Formulation Development and Evaluation of Immediate Release Tablet of Linagliptin"

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ABSTRACT

The present study work aimed to formulate and evaluate an immediate-release tablet anti- diabetic drug for managing diabetes mellitus type 2.

Linagliptin is a selective inhibitor of the enzyme dipeptidyl peptidase metabolizes the naturally occurring incretions- peptide insulin tropic polypeptide resulting in enhanced glucose in the pancreas and decreased hepatic glucose production. Immediate release tablet of Linagliptin prepared by direct compression method. Tablets were prepared using excipients such as microcrystalline cellulose, Lactose monohydrate, Croscarmellose sodium, & Magnesium stearate in different ratios by the direct compression method. The Compatibility of drug and excipient studies showed no interaction between drug and excipient. The prepared formulations show satisfactory results when subjected to various physicochemical tests such as weight of variation, Hardness, thickness, disintegration Time, Friability**,** and Assay**.** The formulations were also subjected to evaluation of in vitro drug release by using US Dissolution Apparatus II. Optimized formulation F6 showed in-vitro release above 85% at the Q time point. The individual steps were improved for the same and the scale-up contemplation has been engaged into account to certify the product performance at pilot plant-up to commercial scale-up.

Keywords: Linagliptin, Anti-diabetic drugs, Compatibility, Immediate-release table.

1. Introduction

Pharmaceuticals have made a major contribution to improving the health status of patients over the past few decades. At the same time, its expenditure has increased rapidly, with spending on medicines outpacing economic growth in many countries. Many economists have speculated that, if spending on healthcare continues to increase at the current rate, the economies of most countries will be severely affected. Most governments have, therefore, begun to implement cost-containment measures to slow the rate of healthcare spending and have concentrated to a larger degree on pharmaceutical spending. Since generics are usually marketed at substantially lower prices than the original brand-name products and, with the rising cost of healthcare; this has made them an attractive option to healthcare providers and governments.

The oral route is the most common and popular route of administration of drugs is the oral route because of its systemic effect, patient compliance, and less expensive to manufacture. The tablet provides high-precision dosing. Tablet form is the most widely used dosage form because of self-administration and ease of manufacturing. In most of the cases immediate set of actions is required as compared to conventional therapy. To achieve the rapid onset of action and eliminate the drawbacks of conventional therapy immediate release dosage form is nowadays popular and used as an alternative oral dosage form. Immediate-release tablets are very quickly after administration. The basic approach used in development is the use of super disintegrants which provide rapid disintegration of the tablet after administration.

TYPES OF TABLETS: [2, 3, 4]

a) **Tablets ingested orally**

a) Standard Compressed tablet b) Multiple compressed tablet c) Repeat action Tablet

d) Delayed action and enteric coated Tablet e) Sugar and chocolate coated tablet

f) Film coated tablet g) Chewable Tablet h) Targeted tablet

2. Tablets used in the oral cavity:

a) Buccal b) Sublingual c) Troches and Lozenges d) Dental cones e) Mouth dissolved

3. Tablets administered by other routes:

a) Implantation Tablet b) Vaginal Tablets

4. Tablets used to prepare the solution:

a) Effervescent Tablet b) Dispensing Tablet c) Hypodermic Tablet d) Tablets Triturates

2. AIM AND OBJECTIVE

Aim: - Formulation, development and evaluation of immediate release tablet of Linagliptin

- **Objectives of Study**

The study has been designed to develop immediate-release tablets of Anti-diabetic agents which would enhance the absorption and bioavailability of the drugs using super disintegrantsby direct compression method. It includes the selection and optimization of suitable excipients for the development of immediate-release tablets for the treatment of diabetics.
The objectives of the present study were.

1. To perform pre-formulation studies.
2. To formulate and develop immediate-release tablets.
3. To achieve optimum homogeneity and physical stability of the formulation.
4. To design and develop an optimized formulation
5. To evaluate the physical and chemical characteristics of the manufactured formulations.
6. To perform in vitro dissolution studies.
7. To perform the stability studies on the finalized formula.
8. To develop an effective, stable, and robust formulation

- **Need of the study**

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration
i.e. the drug-delivery system should deliver the drug at a rate dictated by the needs of the body over a specified

period of treatment. The two most important aspects of drug delivery are spatial placement and temporal delivery of a drug. Spatial placement relates to the targeting a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An appropriately designed drug-delivery system can be a major advance toward solving these two problems. Immediate-release formulation is an important program for new drug research and development to meet several unmet clinical needs.

3. Plan of Work

Phase I

Regularly Literature Survey related to the proposed research topic will be carried out until the last phase of the work

Phase II

1) Selection of Suitable Excipient(s)

2) Development of Linagliptin for tablet manufacturing

3) Preliminary trial batches of Linagliptin tablet and its evaluation

Phase III

Development of Immediate release tablet formulation of Linagliptin

Phase IV

Evaluation of Immediate release tablet formulation:

1. Pre-compression parameters: Bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio etc.

2. Post-compression parameters: hardness, friability, uniformity of weight, drug content and in- vitro dissolution studies etc.

Phase V

Thesis Writing/ Publications/ Patents

Thesis writing of the proposed work will be carried out on the basis of results, publications or patents will be drafted and submitted in to reputed research journals in stipulated time.

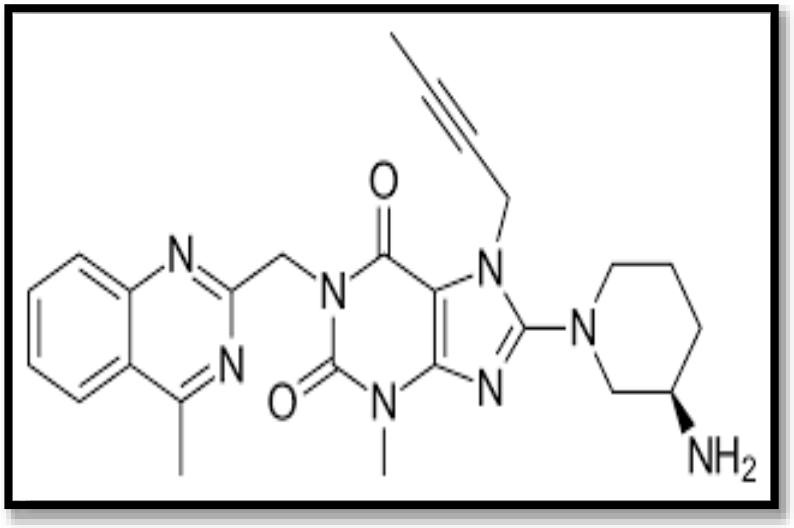
4.1 DRUG PROFILE[40]:-

Drug Name: Linagliptin

IUPAC Name: 8-[(3R)-3-aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-ethylquinazolin-2-yl)methyl]-2,3,6,7-tetrahydro-1H-purine-2,6-dione

Molecular Formula: $C_{25}H_{28}N_8O_2$ **Molecular Weight:** 472.54 g/mol **Category:** Anti-diabetics

Molecular Structure:



Appearance: Linagliptin is an odorless, white, crystalline powder.

Solubility: Soluble in methanol; sparingly soluble in ethanol; very slightly soluble inisopropanol, and alcohol.
Melting Point: 197°-200°C.

BCS class: - III (high solubility, low permeability)

Half-Life: The terminal half-life of linagliptin is 8.6 to 23.9 hours.

PKa: 9.86 (Strongest Basic). **Bioavailability:** - Up to 30% **Protein Binding:** - 90 to 99%
Volume of distribution: - A single I.V. dose of 5mg (1110L^3), I.V. infusion of 0.5-10mg (380-1540LQ)
Route of Elimination: - Urine (5.4%), feces (84.7%)

Clearance: - 374ml/min^2

Storage: Preserve in tight containers, and store at controlled room temperature.

5. Material & Methods[75]:

5.1.1 Material used:

Table 5.1: List of API, excipient with grade and source

Sr. No	Ingredient	Functions	Grad	Source
1	Linagliptin	Active ingredient	-	Laurus lab
2	Lactose monohydrate	Binder	Super tab 11D	DEF pharma
3	Microcrystalline cellulose	Diluent	Avicel 101	FMCbiopharm
4	Cross carmellosesodium (Croscarmellosesodium)	Super disintegrant	Ac-di-sol	Hyqual
5	Sodium starch glycolate (Co-processed starch)	Super disintegrant	Primogel	Hyqual
6	Magnesium stearate	Lubricant	-	Avantor
7	Sodium stearyl fumarate	Lubricant	-	Hyqual
8	Opadry White	Colour	-	Sensient

5.1.2 Instrument used:

Table 5.2: List of instruments with make

Sr. no.	Instruments/ Apparatus	Make
1	Analytical Balance	Sartorius BT2245
2	Moisture analyzer	Sartorius MA150
3	Octagonal blender	Karnawatieng. Ltd
4	Compression machine	Lab India
5	Tablet hardness tester	Lab India
6	Disintegration test apparatus	Electro lab
7	Friability test apparatus	Electro lab
8	Density measurement apparatus	Electro lab
9	Tablet coating machine	Neocoata
10	U V spectrophotometer	Lab India
11	Dissolution test apparatus	Lab India
12	HPLC	waters

5.2 Method Used[88]

5.2.1 Pre-formulation study

Organoleptic properties:-

An Organoleptic property such as colour, odour, taste and appearance of API was observed.

Identification of pure drug:-

Identification of API was carried out by melting point determination, and UV spectroscopy.

Melting point determination:-

The melting point was determined by taking a small amount of API in a capillary tube closed at one end. The capillary tube was placed in an electrically operated melting point apparatus and the temperature at which the drug melts was recorded. This was performed thrice and t h e average value was calculated.

Particle size determination:-

The particle size of API is determined by using a Malvern particle size analyzer.

Loss on drying:-

Loss on drying was carried out by using a halogen moisture analyzer at 105˚C.

5.2.2 Determination of λ max and a calibration curve of Linagliptin:-

Preparation of diluent:

Mixed water and acetonitrile in the ratio of 60:40v/v mixed well. Linagliptin solution was prepared in a diluent, suitable concentration of the drug prepared. The UV spectrum of the solution was taken on a UV/Vis double-beam Spectrometer. The solution exhibited UV maxima at 289 nm.

Calibration curve:-

Weighed and transferred 50 mg of linagliptin 100 ml clear, dry volumetric flask and sonicated for 10 min to dissolve and make up the final volume up to 100 ml with diluent to prepare stock solution. The 0.8 ml of stock standard solution was further diluted in 100 ml with diluent to get 4 µg/ml (working standard). Then 0.6, 0.8, 1.2, 1.6, 2 and 2.4 ml standard in to 100 ml Volumetric flask and made up the volume with diluent to prepare 3,4,6,8, 10 and 12 µg/ml solution. Then the absorbance was measured at 289nm, used diluent as a blank.

5.2.3 BCS solubility study:-

The solubility of drug in various solvent was determined by using shake flask method. Excess amount of API can added into 250ml conical flask containing different types of media such as water, 0.1N HCL, pH 4.5 acetate buffers, pH 6.8 phosphate buffer, pH 7.5 phosphate buffer the shaking process was carried for 24 hours by keeping the conical flask on rotator shaker at 200 rpm. A portion drug dissolved was filtered through (0.45µm) and concentration of drug in the filtrate wasdetermined by HPLC method.

5.2.4 Micrometrics properties of drug and blend:-

Bulk Density:-

It refers to the packing of particles. Bulk density is used to determine the amount of drug that occupies the volume in g/ml.

The bulk density of the ingredients was evaluated using a graduated cylinder. It is the ratio of the total mass of powder to the bulk volume of powder. It was measured by pouring the weighed quantity of powder into a graduated measuring cylinder and the volume was noted. It is expressed in g/ml andis calculated by using the

following formula

Bulk density (ρi) = Mass of the powder (M)/ Volume of the bulk powder (Vb)……. (1)Tapped density:-

It is the ratio of the total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder 10, 500, and 1250 tablets in the tap density apparatus (Electro Lab USP II) according to USP. The blend was subjected to 500 taps; the % Volume variation was calculated and subjected to an additional 1250 taps, % variation was calculated.

Tapped volume (ρt) = Mass of the powder (M) / Tapped volume of the powder (VT). (2)

Compressibility index (Carr's index):-

The compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible material the more flowable it is. A material having values of less than 20% is defined as a free-flowing material. The relationship between % compressibility indexes with flow ability can be given in the table

Compressibility index = Tapped density – Bulk density / Tapped density ×100…… (3)

Table 5.3: Scale of flow ability

% Compressibility	Flow ability	Hauser Ratio
5-15	Excellent	1.00–1.11
12-16	Good	1.12–1.18
18-21	Fairley acceptable	1.19–1.25
23-35	Poor	1.26–1.34
33-38	Very poor	1.35–1.45
< 40	Very very poor	1.46–1.59

Hausner's ratio:-

It indicates the flow properties of the granules and is measured by the ratio of tapped densityto the bulkdensity.

Hausner's ratio = Tapped density /Bulk density..... (4)

Angle of repose:-

The angle of repose is the maximum slope angle of non-cohesive material. For the determination of the angle of repose of powder a ruler, a stand, a funnel, and a tape was used. The powder was allowed to flow through the funnel fixed to a stand at a definite height, usually 10cm. The angle of repose (θ) was then calculated by measuring the height (h) and radius(r) of the heap of granules formed.

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

5.2.5 Drug Excipient Compatibility Study:-

Physical compatibility:

Physical incompatibility is very common in dosage form and is also difficult to detect. It may and may not involve chemical changes, thus permitting the components in formulation to retain their molecular structure. Physical incompatibility involves changes in dissolution, solubility, sedimentation rate, etc. The primary objective of this investigation was to identify a stable storage condition for a drug in a solid state and identification of compatible excipients for its formulation. In this method, different excipients were selected and mixed separately with the drug in a proportion generally used for tablet formulation.

Table 5.4: API/ Excipients name with ratio

Sr. No.	API/ Excipient Name with Grade	Drug: Excipient Ratio
01	API	1
02	API + Microcrystalline Cellulose	1:3
03	API + Lactose Monohydrate.	1:8
04	API + Croscarmellose sodium.	1:2
05	API + Sodium starch Glycolate.	1:0.5
06	API + Sodium stearyl fumarate.	1:0.2
07	API + Magnesium stearate.	1:0.2
08	API + Opadry White	1:1
09	API + All excipient	1:1

FTIR spectroscopy:-

The drug linagliptin and the excipients interaction studies were performed by checking physical appearance as well as using the FTIR analytical method. The interaction studies were done to assess any type of interaction of the drug linagliptin with that of excipients utilized in the development of immediate-release tablet formulation of linagliptin.
An FTIR spectrophotometer was utilized for the infrared analysis of the sample. Around 4-5mg of the sample was properly mixed with dry potassium bromide, and then the sample was analyzed over wave no ranging from 4000 to 400 cm^{-1} at transmission mode

5.2.6 Product Development[92]:

The objective of the project was to develop stable generic impartibility studies, selection of process and equipment, optimization trials and bio-equivalent studies. To develop a bio- equivalent generic formulation of a selected drug candidate, the initial requirement was to choose a suitable manufacturing process.

Manufacturing Process:

The direct compression approach was the development of linagliptin immediate-release tablet 5 mg. Based on the target product profile, evaluation of physiochemical properties of the drug substances and other ingredients, literature search & scientific process below manufacturing process were carried out the development lab scale trial were performed to determine the manufacturing process parameters suchas blending compression and coating. The ultimate goal of the experimentation was to obtain a product that would give a satisfactory in vitro dissolution profile.

Selection of Excipient:

The types of Excipients selected for a formulation depend on the basic process used to manufacture the tablets. The selection of Excipients was done considering the process selected
i.e. for direct compression and literature review. The grade and physical characteristics and properties of the inactive Excipients were selected accordingly. All the Excipients used in the development trials are suitable for direct compression. The results of the stability studies for the API, in conjunction with the API compatibility with the proposed inactive Excipients, justified the selection of the formulation composition

Manufacturing Steps:

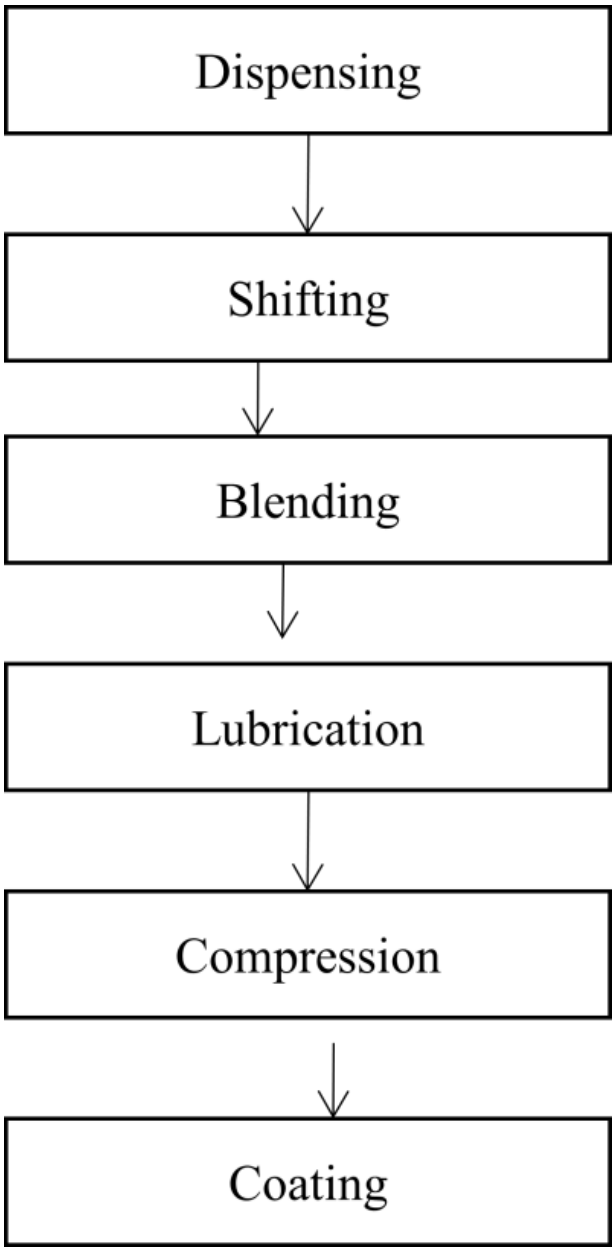


Table 5.5: Manufacturing process

Step No	Process
1.0	**Dispensing**
1.1	API, Microcrystalline cellulose (Avicel PH102), Lactose monohydrate (SuperTab SD11), Croscarmellose sodium (Ac-Di-Sol SD 711), & Magnesium stearate (Hyqual) was dispensed
2.0	**Sifting**
2.1	API, Microcrystalline cellulose (Avicel PH102), Lactose monohydrate (SuperTab SD11) and Croscarmellose sodium (Ac-Di-Sol SD 711) was sifted through sieve #40 and placed separately in polybag
2.2	Magnesium stearate (Hyqual) sifted individual through #60 and placed separately in a polybag
3.0	**Blending & Lubrication**
3.1	Sifted material obtained from above step 2.1 was blended for 20 min. in octagonal blender at 12 rpm
3.2	Sifted magnesium stearate (Hyqual) from step 2.2 added to step no 3.1 and lubricated for 5 minutes in an octagonal blender at 12 rpm
4.0	**Direct Compression**
4.1	The lubricated blend from step3.2 was compressed into tablets by using suitable punch tooling using a compression machine
5.0	**Coating**
5.1	Opadry white was added in Purified water with stirring, stir the solution for 45 minutes and filter through #100 mesh
5.2	Core tablets from step5.0 were coated by using a coating solution in coating machine until 3.00 %w/w weight gain achieved

Coating Parameter:

Preparation of coating solution:

Opadry White: 6mg/tab

Purified water: Q.S

The dispersion was prepared using a mechanical stirrer and kept under the stirrer in 45 min. It wash then filtered through a nylon cloth.

Table 5.6: Coating process parameter

Inlet temp.	50-55ºC
Bed temp.	42ºC
Exhaust temp.	40-45ºC
Pan rpm	2-6 rpm
Atomization	1.2 bar
Spray rate	5gm/min

Table 5.7: Different trail formulation of Linagliptin Tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
	Quantity of mg per Tablet								
Linagliptin	5	5	5	5	5	5	5	5	5
MCC PH101	10	10	10	10	10	10	10	10	10
Lactose monohydrate	170	165	160	170	165	160	170	165	160
Cross carmallose sodium	10	15	20	-	-	-	5	7.5	10
Sodium Starch Glycolate	-	-	-	10	15	20	5	7.5	10
Sodium stearyl fumarate	3	3	3	3	3	3	3	3	3
Magnesium stearate	2	2	2	2	2	2	2	2	2
Core Tablet Wt.	200	200	200	200	200	200	200	200	200
Opadry White	6	6	6	6	6	6	6	6	6
Coated Tablet Wt.	206	206	206	206	206	206	206	206	206

5.2.7 Procedure:

Table 5.8: Inject 20µl of solution as per the sequence below

Sr. No.	Description	No. of injection
1	Blank	1
2	Standard solution	6
3	Sample solution	2
4	Bracketing Standard Solution	1

% Content = (AT/AS) x (WS/100) x (5/50) x (200/20 Tablet) x (50/5) x (P/100) x (100/LC)

AT: average peak area of Linagliptin in the chromatogram of sample solution AS: average peak area of Linagliptin in the chromatogram of standard solution
WS: weight of Linagliptin standard in mgP: % potency of Linagliptin standard
LC: label claim of Linagliptin per tablet in mg

5.2.8 Dissolution method:-

In vitro dissolution study was carried out for optimized formulation of Linagliptin Tablet and reference standard in pH 6.8 phosphate buffer. The temperature of the dissolution medium was maintained at 37 ± 0.5°C and the drug concentration was determined by HPLC method.

Procedure:

Preparation of Dissolution Media:

Weigh and transfer 6.8gm of potassium dihydrogen phosphate and 8 mg of Sodium hydroxide in 10000 ml of water, and mix to dissolve. Adjust pH 6.8 with diluted sodium hydroxide, mixed well.

Dissolution Parameter:

Apparatus	USP TYPE II(Paddle)
Media	Buffer pH 6.8 phosphate buffer.
Speed	50RPM
Temperature	37◦C (± 5◦C)
Media Volume	900mL
Time Point	5, 10, 15, 20, 30, 45 minutes
AcceptanceCriteria	Not less than 80% (Q) of the labelled amount of the drug is Dissolved in 15 minutes

Preparation of Buffer for mobile phase:

Dissolve 1.36 gm. of potassium dihydrogen phosphate in 1000 ml of water. Mixed well to dissolve. Adjust pH 3.2 with orthophosphoric acid. Filter the buffer solution through a 0.45µm nylon membrane filter.

Preparation of Mobile Phase:

Prepare a mixture of buffer pH 3.2 and Acetonitrile in the ratio 750:250 v/vrespectively, mix and degas

Preparation of Diluents: Use dissolution media as diluents.

Chromatographic Condition:

Column	**Zorbax SB CN150x 4.6mm,3.5µm**
Flow Rate	1.0ml/ minute
Injection Volume	50 µl
Wavelength	289nm
Colum Temp	40^0 C
Sample Temp	25 ^{0} C
Run Time	7 Min
Retention Time	About 3.8 minutes
Needle wash	Water: Acetonitrile, 10 :90v/v

Preparation of Standard Stock Solution:

Weigh accurately about 35.0 mg Linagliptin working standard and transfer into 100 ml volumetric flask. Add 70ml dissolution media, sonicate to dissolve, and make up the volume up to mark with media. Further, dilute 4 ml of the stock solution into the 250 ml volumetric flask. With dissolution media. Mixed well.

Preparation of Sample Solution: Set the dissolution apparatus as per parameter. Place one tablet in each dissolution vessel and carry out the dissolution. Withdraw 10.0 ml of solution as per the set intervals of time and replenish the same with fresh 10.0 ml dissolution media. Inject the filtered aliquot in a chromatographic system.

Calculation:

Calculate the % release of Linagliptin present in the tablet as given below:

% Content = (AT/AS) x (WS/100) x (4/250) x (900/1 Tablet) x (P/LC)Where,
AT: average peak area of Linagliptin chromatogram of sample solution

AS: average peak area of Linagliptin chromatogram of standard solution

WS: weight of Linagliptin standard in mg

P: % potency of Linagliptin standard

LC: label claim of Linagliptin per tablet in mg

6.2.10 Dissolution profile comparison:

It is model independent approach using similarity factor. A comparative dissolution profile is used to demonstrate the equivalence of any change in the formulation of the drug.

Dissimilarity factor (f1)

Dissimilarity factor describe the relative error between two dissolution profiles. It approximately gives the error between curves reference profile are identical and increase proportionally with the dissimilarity between the two profiles.

Dissimilarity factor (f1) was calculated from the following equation

$$f_1 = \left\{ \frac{\left\{ \sum_{t=1}^{n} |Rt - Tt| \right\}}{\sum_{t=1}^{n} Rt} \right\} \times 100$$

Where,

n = number of time point

R_t = % dissolved at time t of reference product

T_t = % dissolved at time t of the test product

The dissimilarity factor (f1) should be between 0 to 15

Similarity factor (f2): - The resulting dissolution profile was compared to the targeted profile using the Food Drug Administration (FDA) recommended model-independent approach utilizing the similarity factor (f2). This similarity factor is an algorithmic reciprocal square root transformation of the sum of squared errors, and it serves as a measure of the similarity of two respective dissolution profiles

Similarity factor

(f2) =50 log {[1+1/nΣ (Rt−Tt) 2] −0.5×100} nt = 1..... (8)

Where,

Rt and Tt = % of drug which was dissolved at each time point for the test and referenceproducts respectively.
n = number of time points considered.

FDA has set a standard of f2 value between 50-100 to indicate similarity between twodissolution profiles.

6. RESULT AND DISCUSSION

6.1 Physiochemical properties of the drug:-

6.1.1 Organoleptic properties:

Table 6.1: Organoleptic properties of API

Properties	Observation
Colour	White to off-whitepowder
Taste	Bitter
Odor	Odorless
Appearance	Off white Powder

6.1.2 Melting point determination:-

The melting point of API was found to be in the range given in the literature (197- 200ºC).Hence the drug can be stated as pure.

Table 6.2: Melting point determination

Sr. No.	Melting point [˚C] (observed)	Average [˚C]
1	200	199
2	198	
3	200	

6.1.3 Solubility:-

The solubility of the received sample of API was examined in various solvents (aqueous andorganic). It is only a qualitative analysis. The results thus obtained were as follows-

Table 6.3: Details of solubility of API

Sr. No.	Solvent	Solubility
1	Alcohol and Water	Freely soluble
2	Methylene chloride	Very slightly soluble

6.1.4 Particle size determination:-

Sample of API was analyzed by using Malvern particle size analyzer, particles were found infollowing size ranges

Table 6.4: Particle size determination

Sr. No.	Diameter	Particle size(µm)
1	D10	12.4
2	D50	49.8
3	D90	123.1

Absorbanc

6.1.5 Loss on drying :-

Loss on drying was carried out by using a halogen moisture analyzer and it was found to be 0.51%at 105ºC

6.2 Determination of λ max:

6.2.1 Ultraviolet absorption spectroscopy:Wavelength Selection:

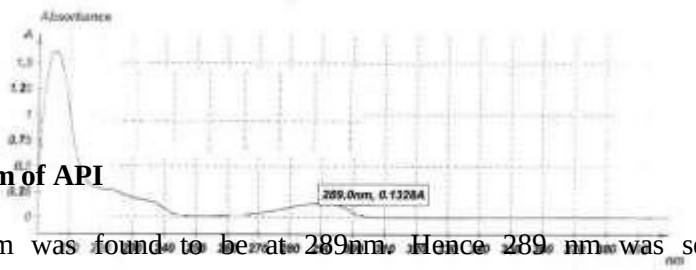


Figure 6.1: UV Spectrum of API

An absorption maximum was found to be at 289nm. Hence 289 nm was selected as λ max forfurther studies.

6.2.2 Calibration curve for Linagliptin:

The solution containing different concentrations of Linagliptin was prepared and scanned at 289 nm by using a UV spectrophotometer. The graph of absorbance vs. concentration was plotted and found to be linear over the range of 3-12µg/ml indicating its compliance with Lambert's-Beer's law.

Table 6.5: Absorbance at various cons. of Linagliptin

Sr. No.	Concentration(µg/ml)	Absorbance
1	0	0
2	3	0.1008
3	4	0.1314
4	6	0.1952
5	8	0.2624
6	10	0.3239
7	12	0.3951

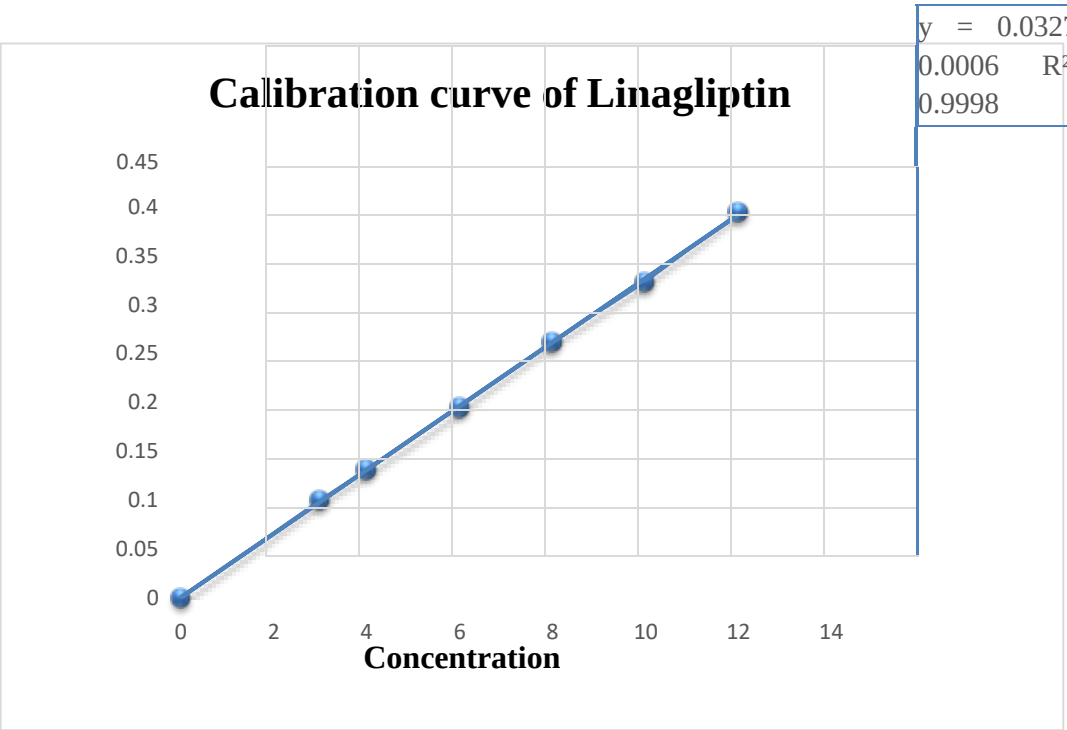


Figure6.2: Calibration curve of the drug in water and Acetonitrile

Table 6.6: Parameters found in calibration curve

Sr. No.	Parameter	Finding
1	Wavelength detection	289 nm
2	Regression equation	y = 0.0327x+0.0006
3	Correlation coefficient	R = 0.9998

6.3. BCS solubility study:-

Table 6.7: BCS solubility data of Linagliptin in different media

Sr.No	Media	mg/250ml
1	Purified Water	3.2
2	0.1N HCl	1.8
3	pH 4.5 Acetate buffer	2.8
4	pH 6.8 phosphate buffer	4.8
5	pH 7.5 phosphate buffer	4.2

6.4 Micrometrics properties evaluation:

Table 6.8: Micrometrics properties of Linagliptin

Sr. No	Parameters	Results	Flow properties
1	Bulk density(g/ml)	0.62	-
2	Tapped density(g/ml)	0.78	-
3	Carr's index (%)	19.95	Fairly acceptable
4	Hauser's ratio(H_R)	1.23	Fairly acceptable
5	Angle of repose(θ)	28	Good flow properties

6.5 Drug-Excipients Compatibility Result:

Physical compatibility:

Table 6.9: Result of physical compatibility of Drug

Sr. No.	API/ Excipients Name with Grade	Drug: Excipient Ratio	Initial Condition	observationson appearance
01	API	1	White	No change
02	API +Microcrystalline Cellulose	1:3	White	No
03	API +Lactose Monohydrate	1:8	White	change
04	API + Sodium starch glycolate	1.0.5	White	No
05	API + Croscarmellose sodium	1:2	White	change
06	API +Sodium stearyl fumarate	1:0.2	White	No
07	API + Magnesium stearate	1:0.5	White	change
08	API + Opadry Orange	1:1	White	No
09	API + All excipient	1:1	No colorchange	change

Conclusion:

No change was observed in any of these mixtures at Initial in open condition. There is no incompatibility with the selected excipients.

FTIR Spectroscopy:

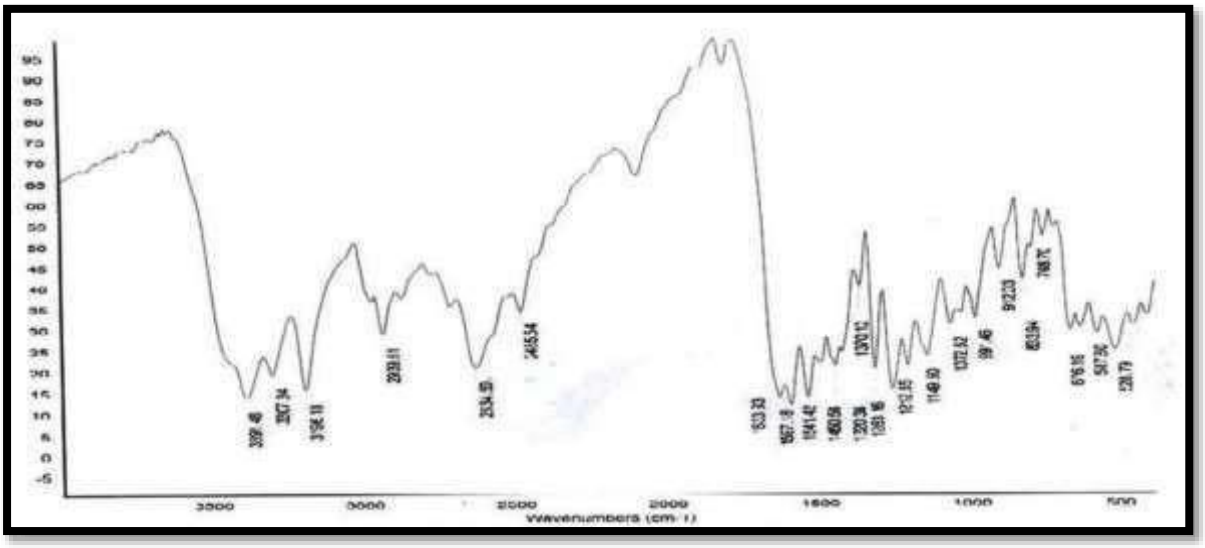


Figure6.1: FTIR Spectrum of Linagliptin

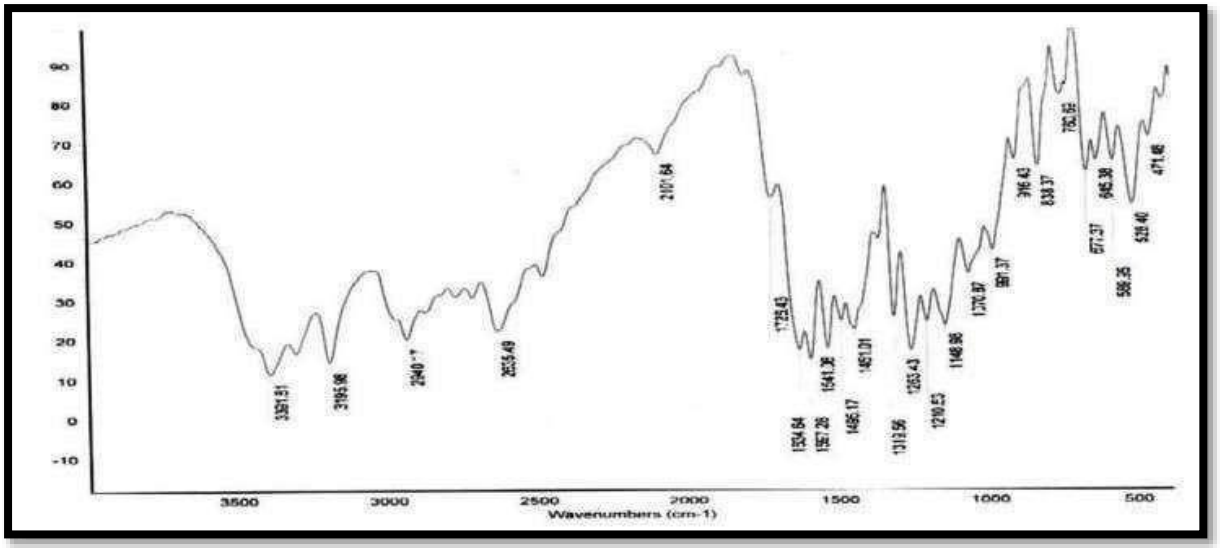


Figure6.2: FTIR Spectrum of Linagliptin & CCS

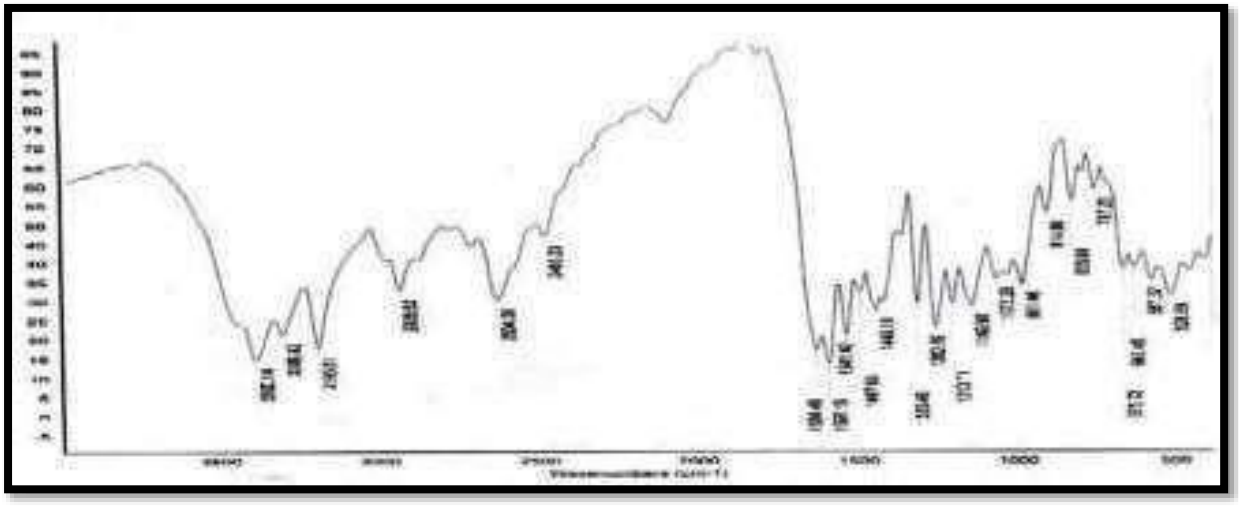


Figure6.3 FTIR Spectrum of Linagliptin & SSG

Table 4: Wave Numbers of FTIR peaks of Linagliptin + excipients:

FTIR Samples	Peak Values (Wave Number) (cm-1)
Linagliptin	3391.48, 2634.50, 1597.18, 676.19
Linagliptin and CCS	3390.14, 2634.09, 1597.15, 643.48
Linagliptin and SSG	3391.81, 2635.49, 1597.28, 589.95

Conclusion:

FTIR studies were conducted for Linagliptin alone and a combination of super disintegrating agents and Linagliptin to determine any interaction between the drug and super disintegrants. The characteristics peak for Linagliptin (3391.48, 2634.50, 1597.18, and 676.19) and Linagliptin with super disintegrants were identified and no notable shift in characteristics peak was observed. So it was concluded that there was no interaction between drugs and super disintegrants.

6.6 Pre compression parameter:-

Table 6.11: Evaluation of lubricated blend

Formulation.no	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility y index (%)	Hausner ratio (HR)	Angle ofrepose (θ)
F1	0.543	0.718	16.38	1.18	29.37
F2	0.588	0.734	15.05	1.17	28.22
F3	0.600	0.749	14.65	1.22	27.37
F4	0.598	0.742	15.49	1.21	28.23
F5	0.610	0.780	14.28	1.16	27.31
F6	0.618	0.791	13.43	1.18	25.22
F7	0.621	0.773	14.65	1.16	30.17
F8	0.590	0.764	15.97	1.18	29.19
F9	0.597	0.759	17.04	1.17	28.88

Conclusion:

In the above table characteristic of the powder blend from F1 to F9 is given. From values of Compressibility index and Hauser's ratio we can conclude that blend of the above formulation have passable flow properties and compressibility index.

. **6.7 Physical evaluation of formulated tablet:**

Specification	Linagliptin tablet
Colour	White colour
Size and shape	Round shape with one side break line
Thickness	2.72 to 3.18 mm
Hardness	2.6 to 3.8 kg/cm^3

6.8 Post compression Parameter:

Table 6.12: Evaluation of Post compression Parameter

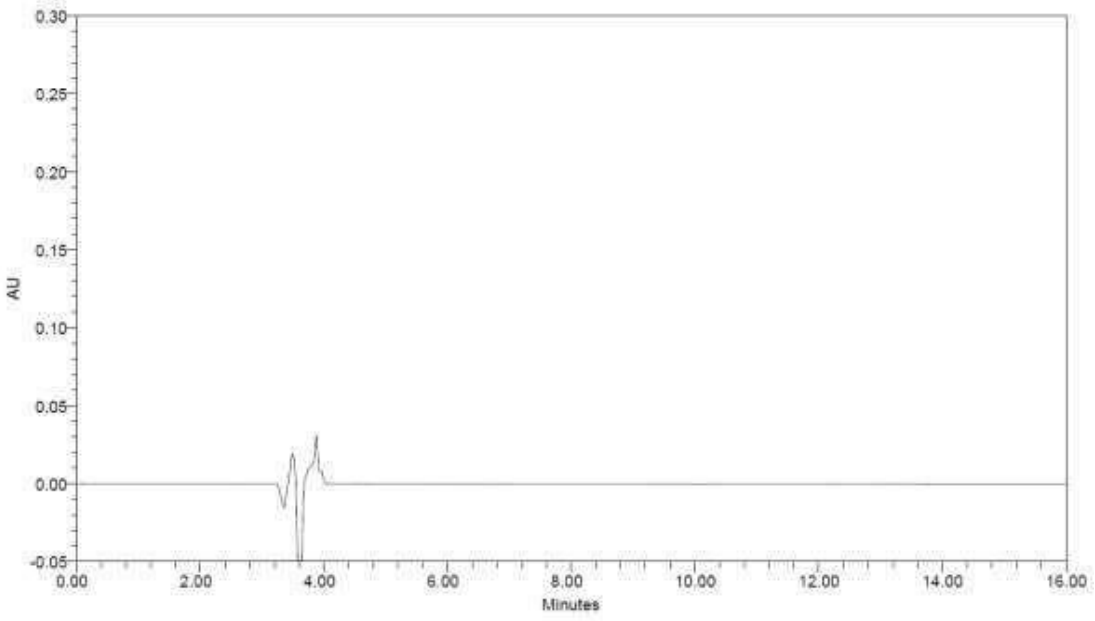
FormulationNo	Weight Variation (mg)	Hardness (kg/cm^3)	Thickness (mm)	Disintegration Time (sec)	Friability(%)	Assay (%)
F1	205.2	2.7	2.95	105	0.4	97.8
F2	205.6	2.8	3.02	100	0.4	97.9
F3	206.2	2.6	3.09	98	0.5	97.9
F4	205.4	3.8	3.13	65	0.3	98.9
F5	205.5	3.7	3.17	60	0.2	99.5
F6	205.8	3.6	3.18	51	0.1	99.6
F7	205.1	2.6	2.72	90	0.3	98.2
F8	205.3	2.8	3.13	88	0.3	98.9
F9	206.1	2.9	3.15	70	0.2	99.4

Conclusion:

From among all the nine comparisons, batches with the variable Disintegrates formulation batch no. F6 was found to be satisfactory as compared to other formulations. In this, the thickness, hardness and disintegration time of the prepared tablet were found to be satisfactory. In the friability test the maximum weight loss should be not more than 1%. The result revealed that the tablets passed the friability test.

7.9 HPLC Method:-

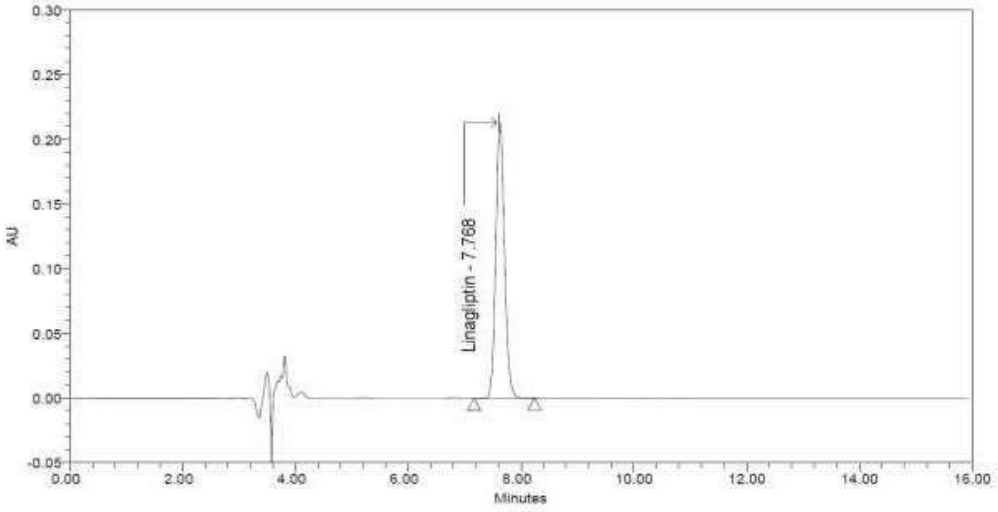
Figure No 6.4: Chromatogram of Blank



Peak Results

	Name	Injection	RT	Area	% Area	Plate Count	Tailing	Purity1 Angle	Purity1 Threshold	Purity1 Flag
1	Linagliptin	1	7.864							No

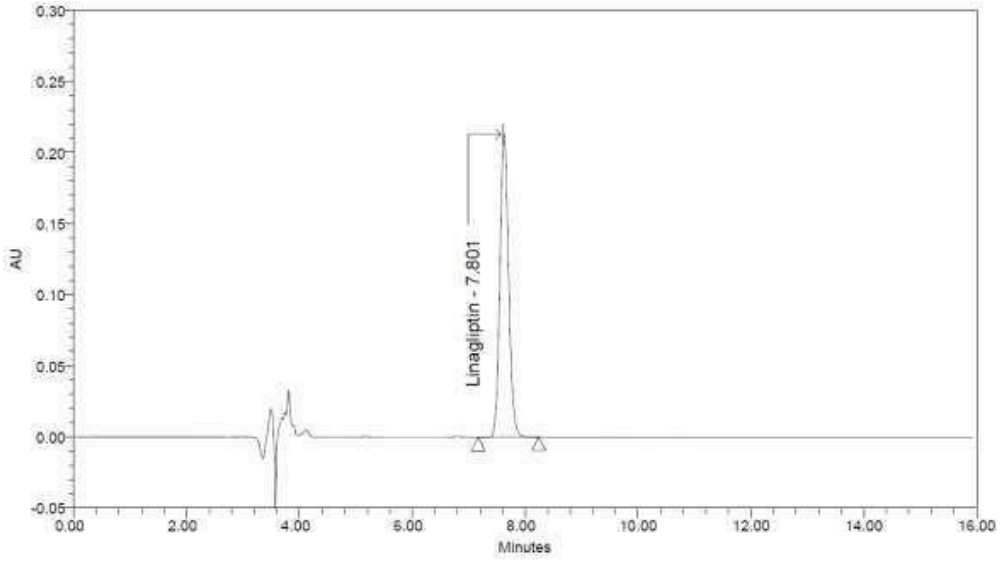
Figure No 6.2: Chromatogram of Standard Solution



Peak Results

	Name	Injection	RT	Area	% Area	Plate Count	Tailing	Purity1 Angle	Purity1 Threshold	Purity1 Flag
1	Linagliptin	1	7.768	738568	100.000	10578	1.3	0.178	1.574	No

Figure No 6.5: Chromatogram of sample Solution



Peak Results

	Name	Injection	RT	Area	% Area	Plate Count	Tailing	Purity1 Angle	Purity1 Threshold	Purity1 Flag
1	Linagliptin	1	7.801	736847	100.000	10457	1.2	0.104	1.357	No

CONCLUSION

Linagliptin is an anti-diabetic drug used for the treatment of type 2 diabetes, it belongs to the class of DPP-4 inhibitors. It has a long half-life of about 8.6-23.9 hours; hence, to achieve immediate therapeutic action, it needs immediate release tablet formulation. Among the various techniques using super disintegrants is a simple approach to formulate immediate-release tablets. The objective of the present work is to formulate and evaluate a better formulation and to provide a tablet dosage form with satisfying parameters for the Linagliptin immediate-release tablets including pre-formulation studies. The prepared tablets were evaluated for physical properties and in-vitro dissolution studies. Compatibility studies of Linagliptin and excipient have been done by FTIR.

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