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"FORMULATION & EVALUATION OF LISINOPRIL IMMEDIATE RELEASE TABLET"

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ABSTRACT:

The objective of the study was to develop an immediate release tablet formulation of lisinopril and evaluate it. Different formulations were prepared by varying the concentration of the drug and excipients using the direct compression method. The tablets were evaluated for various physical parameters such as hardness, friability, and disintegration time. Among the different formulations, F3 was found to have the best results in terms of drug release profile, disintegration time, and other parameters. The in vitro drug release of the optimized formulation (F3) was found to be 98% within 30 minutes.

Keywords: Immediate release tablet, Sodium Starch Glycolate, Lisinopril.

1. INTRODUCTION:

A pharmaceutical preparation that is meant to be consumed by mouth, either whole or after chewing, is referred to as an oral dosage form. These forms, which include tablets, capsules, suspensions, solutions, and syrups, are utilized to provide medication to the body. Because they are simple to use, generally safe, and available in a range of dosages and formulations to meet the needs of varied patient populations, oral dosage forms are a common and practical way to give medication. As the digestive system can swiftly absorb medications from the gastrointestinal tract and transport them throughout the body, they are also a successful method of administering medication to the body. To assist control the quantity of medication that enters the bloodstream over time, oral dosage forms can be created to release medication into the body at various rates. For instance, some pills are made to release medication over the course of many hours, ensuring a continuous and regular flow of the medication into the body. For medications that need a gradual and continuous release to sustain their therapeutic impact over time, this can be very helpful. Overall, oral dose forms are an important part of contemporary medicine and are used to treat a variety of illnesses, from straightforward problems like colds and headaches to more difficult ones like cancer and heart disease. They are an essential component of contemporary healthcare because they let patients to get the medication they require in a convenient, safe, and efficient way.

Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly patient compliance. The development of enhanced oral protein delivery technology by immediate release tablets which may release the drugs at an enhanced rate are very promising for the delivery of poorly soluble drugs high molecular weight protein and peptide. The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance. [1-3]

2. Formulation consideration of Immediate release tablet dosage form:

Formulation considerations for the preparation of immediate release tablets include various factors that can affect the drug's bioavailability, pharmacokinetics, and overall therapeutic effectiveness. The following are some of the critical formulation considerations:

I. **Drug Properties:** The physicochemical properties of the active drug ingredient(s), such as solubility, stability, and particle size, play a crucial role in the formulation process. The drug's properties can determine the choice of excipients, the method of preparation, and the dosage form's overall performance.

II. **Excipient Selection:** The selection of excipients is a critical aspect of immediate release tablet formulation. Excipients should be carefully chosen to ensure compatibility with the active drug ingredient(s), enhance its solubility, facilitate tablet compression, and promote the desired dissolution and disintegration properties.

III. **Manufacturing Method:** The manufacturing method used to prepare immediate release tablets can significantly impact the tablet's performance. The choice of manufacturing method, such as direct compression, wet granulation, or dry granulation, can affect the tablet's physical characteristics, such as hardness, friability, and dissolution rate.

IV. **Tablet Design:** The design of the tablet, such as size, shape, and weight, can impact its performance. The tablet's design can affect its disintegration and dissolution properties, and patient compliance.

V. **Coating:** The use of coating agents can affect the tablet's appearance, taste, and stability. The choice of coating agent can impact the drug release profile and overall bioavailability.

VI. **Regulatory Requirements:** Regulatory requirements, such as safety, efficacy, and stability, must be considered during the formulation process. The choice of excipients and manufacturing methods should comply with regulatory guidelines and standards. [5-8]

3. MATERIALS AND METHODS:

Table 1: Materials

SR. NO.	MATERIAL	SOURCE
1.	Lisinopril (API)	Avantor Pvt. Ltd.
2.	Lactose	Loba Chemie Pvt. Ltd.
3.	Microcrystalline cellulose	Loba Chemie Pvt. Ltd.
4.	Dibasic calcium phosphate	Loba Chemie Pvt. Ltd.

5.	Croscarmellose sodium	Loba Chemie Pvt. Ltd.
6.	Sodium starch glycolate	Loba Chemie Pvt. Ltd.
7.	Magnesium stearate	Avantor Pvt. Ltd.
8.	Colloidal silicon dioxide	Loba Chemie Pvt. Ltd.
9.	Hypromellose	Loba Chemie Pvt. Ltd.
10.	Polyethylene glycol	Loba Chemie Pvt. Ltd.
11.	Titanium dioxide	HiMedia Laboratories
12.	Iron oxide pigments	Loba Chemie Pvt. Ltd.
13.	Aerosil	HiMedia Laboratories
14.	Calcium-Carbonate	HiMedia Laboratories
15.	Di-Calcium Phosphate	HiMedia Laboratories
16.	Gelatin	HiMedia Laboratories
17.	Mg stearate	Avantor Pvt. Ltd.
18.	Propyl paraben	Avantor Pvt. Ltd.

All the chemicals and reagents used were of analytical grade.

Method of Preparation of Tablet: [12-13]

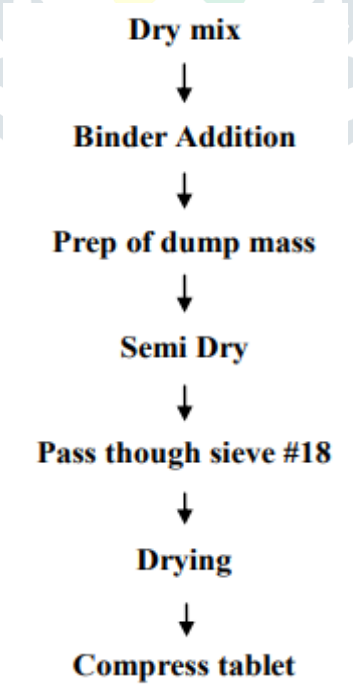

Figure 1: Method of preparation of tablet

Formulation of Lisinopril tablet:

Table 2: Formulation of Lisinopril

Ingredient In Mg	F1	F2	F3	F4	F5	F6
Lisinopril (API)	20	20	20	20	20	20
Lactose	40	40	40	-	-	-
Microcrystalline cellulose	75	75	75	80	80	80
Dibasic calcium phosphate	35	35	35	-	-	-
Croscarmellose sodium	-	-	1	-	2	-
Sodium starch glycolate	76	70	65	55	90	65
Magnesium stearate	8	8	8	8	8	8
Colloidal silicon dioxide	0.8	0.5	0.5	0.6	0.6	0.5
Talc	9	7	8	9	8	8
Hypromellose	-	-	-	2	4	5
Polyethylene glycol	-	-	2	2	-	2
Titanium dioxide	0.1	0.1	0.1	0.1	0.1	0.1
Iron oxide pigments	-	-	-	1	2	4
Aerosil	-	5	5	6	5	5
Calcium-Carbonate	30	32	35	30	30	32
Di-Calcium Phosphate	-	-	-	40	15	40
Gelatin	6	7	5	6	-	-
Propyl paraben	0.1	0.1	0.1	0.1	0.1	0.1
Water	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.

Evaluation:

Flow Properties of Mixture:

I. Bulk density and tapped density: Directly compressible blend was poured gently through a glass funnel into a graduated cylinder of bulk density apparatus. Then Bulk density and tapped density were calculated. [14]

$$\text{Bulk density} = \frac{\text{Weight of sample in gram}}{\text{Final volume of sample contained in cylinder}}$$

$$\text{Tapped density} = \frac{\textbf{Weight of sample in gram}}{\text{Final volume after tapping in cylinder}}$$

II. Carr's compressibility index:

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. According to the theory, the less compressible material is more flowable. A material having values less than 20 to 30% is defined as the free-flowing material, based on the apparent bulk density and tapped density, the percentage compressibility of the bulk drug was determined by using the following formula. It is expressed in percentage and is expressed by[14]

$$\mathbf{I = (Dt - Db / Dt) \times 100}$$

Where:

Dt - is the tapped density of the powder

Db- is the bulk density of the powder.

The compressibility index and Hausner ratio are measures of the products ability to settle, and permit an assessment of the relative importance of interparticulate interactions. In a free-flowing powder these interactions are less significant and the bulk and tapped densities will be closer in value. For poorly flowing materials, there are greater interparticulate interactions and a greater difference between the bulk and tapped densities will be observed. The differences are reflected in the compressibility index and Hausner ratio Compressibility index:

III. Hausner ratio: The flow properties of blend, granules or Powder are measured by this ratio.

$$\frac{V_0}{V_f}$$

V0= unsettled apparent volume (bulk volume) Vf= final tapped volume

As seen in the table below the compressibility index and Hausner ratios can be used to estimate the flow characteristics of the powder. [14]

Table no. 3: Relationship between percent compressibility and Flowability

Compressibility index (per cent	Flow character	Hausner ratio
1-10	Excellent	1.00-1011
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very very poor	>1.60

IV: Angle of Repose:

Angle of repose is used to determine the flow properties of powders, pellets or granules. angle of repose of different formulations was measured by fixed funnel standing method. Microspheres were passed through the funnel up to the tip of funnel, which was kept at a certain height (2.5cm) from horizontal surface. The passed microspheres formed a pile of height 'h' above the horizontal surface. Make 4 points which are opposite to each other on the circular base on the paper. Record diameter & radius &. The angle of repose was determined by[18]

Tan (θ) = h / r Angle of repose (θ) = tan -1 (h / r)

Where,

h = height of the heap

r =Radius of the heap

Table 4. Relationship between angle of repose (θ) and Flowability

Flow property	Angle of repose (degrees)
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Very very poor	>66

Weight Variation:

The weight of the Chewing gum being made was routinely determined to ensure that a tablet contains the proper amount of drug. The IP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablet met the IP specification that not more than 2 tablet are outside the percentage limits and no lozenges differs by more than 2 times the percentage limit. [21]

Hardness

The hardness of each batch of TLM was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm 2. 3 tablet were chosen randomly and tested for hardness. The average values, standard deviation and relative standard deviation were calculated. [21]

Thickness

Thickness was measured using Vernier Calipers. It was determined by checking the thickness and diameter of ten Tablet of each formulation. The extent to which the thickness of each tablet deviated from ± 5% of the standard value was determined. [21]

Drug Content

$$Drug\ content = \frac{Conc.^{n} \times vol. \times DF}{1000}$$

Randomly 10 tablet were taken, crushed and amount equivalent to 5 mg of drug was taken and dissolved in solvent mixture, sonicated, make up volume with solvent mixture, further dilution ,5ml of stock solution take in 50ml of volumetric flask and make up volume with solvent mixture filter the solution and record the absorbance using spectrophotometer at 298nm. Then, drug concentration was measured using standard graph. The measurements were carried out in replicates (n=6). [24]

In-Vitro Release Studies:

The immediate release tablets are subjected to in vitro drug release studies in pH 7.5 phosphate buffer or 0.1N HCl for 30 minutes to access the ability of the formulation for providing immediate drug delivery. Drug release studies were carried out in dissolution test apparatus using specified volume 900ml of dissolution media maintained at 37±0.2C. The tablets are kept in the cylindrical basket or directly placed in medium with paddle then rotated at 100 rpm. 5ml of the sample from the dissolution medium are withdrawn at each time interval (5, 10, 15 & 30 minutes) and 5ml of fresh medium was replaced each time. The samples were filtered and from the filtrate 1ml was taken and diluted to 10ml. These samples were analyzed spectrophotometrically and further calculation was carried out to get drug release. The drug released data were plotted and tested with zero order (Cumulative % drug released Vs time), First order (Log % Remained Vs time). The in vitro dissolution kinetic parameters, dissolution rate constants, correlation coefficient and dissolution efficiency were calculated. [24]

Stability studies of Lisinopril

Stability is defined as the ability of a particular drug or dosage form in a specific container to remain within its physical, chemical, therapeutic, and toxicological specifications. Drug decomposition or degradation occurs during storage, because of chemical alteration of the active ingredients or due to product instability, lowering the concentration of the drug in the dosage form. Stability study of the dosage form must include a section for product characterization and another section to study the product stability during storage. Formulations are evaluated for their appearance, possible weight gain in drug content thickness, flatness, folding endurance, tensile strength, moisture content and moisture uptake, and in-vitro release study by keeping dosage form in different temperature and humidity condition after a specified time. The stability study indicates that the formulation is quite stable at different conditions of storage. [24]

Recommended long-term and accelerated storage conditions

Study Storage condition Minimum time period covered by data at submission Long term-25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH 12 months

Intermediate-30°C ± 2°C/65% RH ± 5% RH 6 months

Accelerated-40°C ± 2°C/75% RH ± 5% RH 6 months

Result:

Characterization of Lisinopril:

Organoleptic characterization and Melting point determination

The physicochemical characteristics of Lisinopril are described in Table 12.

Table 5. Physicochemical Characteristics of Lisinopril

SR. NO	TEST	OBSERVATION
1.	Appearance	White crystalline powder
2.	Color	White to off-white
3.	Odor	Odorless
4.	Taste	Tasteless
5.	Melting point	148-150°C
6.	pH	Aqueous solutions are acidic with a pH of approximately 3.5

The organoleptic character and melting point was found as per the standard drug so drug used in the formulation was found to be pure according to I.P. specification.

Solubility analysis:

Table 6: Solubility profile of Lisinopril

SR. NO.	SOLVENT	SOLUBILITY
1.	Water	Freely soluble, 60 mg/mL at 25°C
2.	Methanol	Sparingly soluble, 2.5 mg/mL at 25°C
3.	Ethanol	Practically insoluble, <0.5 mg/mL at 25°C

4.	Acetone	Practically insoluble, <0.5 mg/mL at 25°C
5.	Ethyl acetate	Practically insoluble, <0.5 mg/mL at 25°C
6.	Chloroform	Practically insoluble, <0.5 mg/mL at 25°C
7.	Diethyl ether	Practically insoluble, <0.5 mg/mL at 25°C
8.	Hexane	Practically insoluble, <0.5 mg/mL at 25°C
9.	Isopropyl alcohol	Sparingly soluble, 2.5 mg/mL at 25°C
10.	Propylene glycol	Sparingly soluble, 1.3 mg/mL at 25°C
11.	Glycerin	Sparingly soluble, 1.0 mg/mL at 25°C

Micromeritic characterization of drug:

The micromeritic characterizations of drug were carried out and the following observations were made.

Table 7: Micromeritic characterization of Lisinopril

SR. NO.	Property	Value
1.	Bulk density	0.4-0.6 g/mL
2.	Tapped density	0.5-0.7 g/mL
3.	Hausner's ratio	1.25-1.40
4.	Carr's index	10-20%
5.	Angle of repose	28-32°
6.	Particle size distribution (D50)	20-50 μm
7.	Surface area (BET)	~1-2 m^2/g
8.	Porosity	~0.3-0.4 mL/g

On the basis of micromeritic properties it was confirmed that the drug Lisinopril possessed sufficient Flowability to be used for compression.

Standard calibration curve of Lisinopril.

Table 8: Standard calibration curve of Lisinopril.

SR. NO.	CONCENTRATION (ug/ml)	ABSORBANCE (at 218 nm)
1.	2	0.0591
2.	4	0.1245
3.	6	0.1891
4.	8	0.2987
5.	10	0.4026
6.	12	0.5112
7.	14	0.6512
8.	16	0.7451

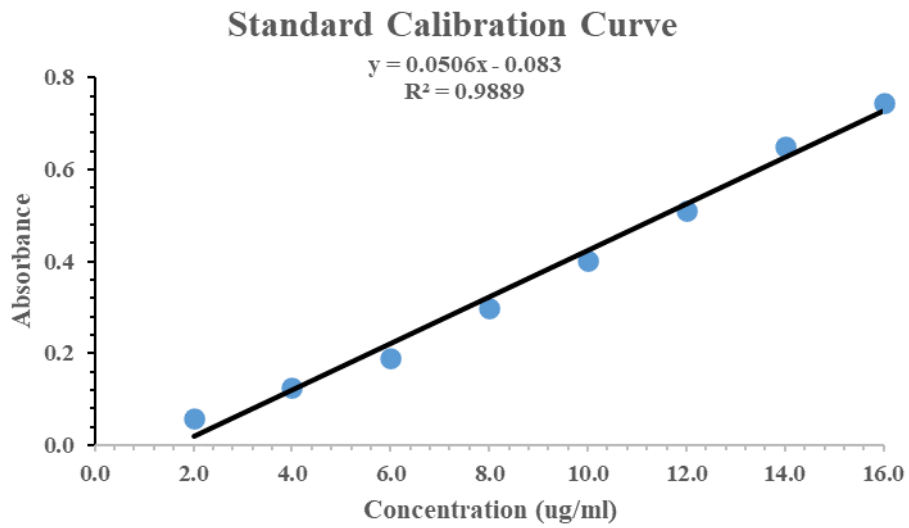

Figure 2 Calibration curve of Lisinopril in Water.

Determination of λ max:

The UV spectrum of Lisinopril in water showed maximum absorption at 218 nm. Hence drug used in the formulation was found to be pure according to I.P. specification. The UV spectrum of the Lisinopril in methanol is given in Figure:

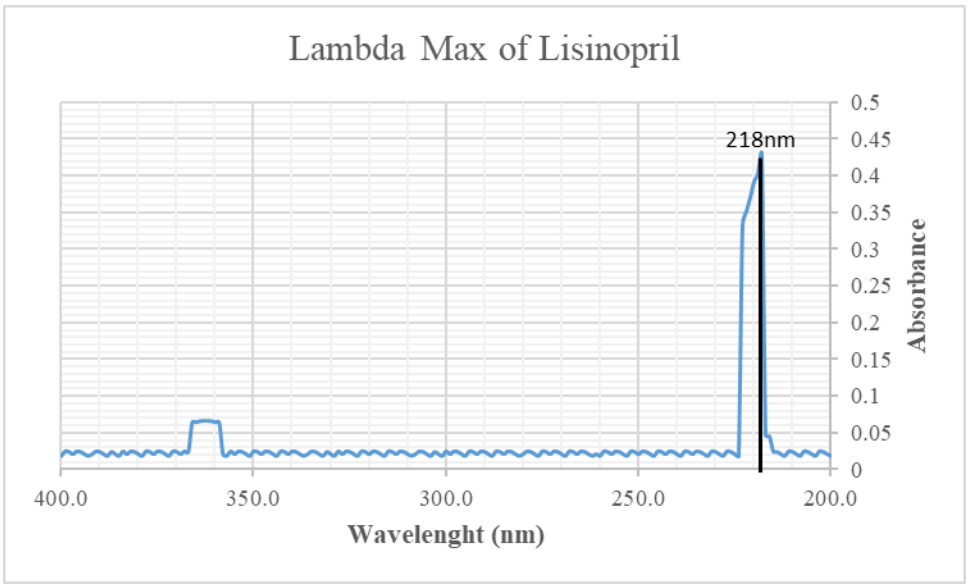

Figure 3: Lambda Max of Lisinopril

FTIR Analysis

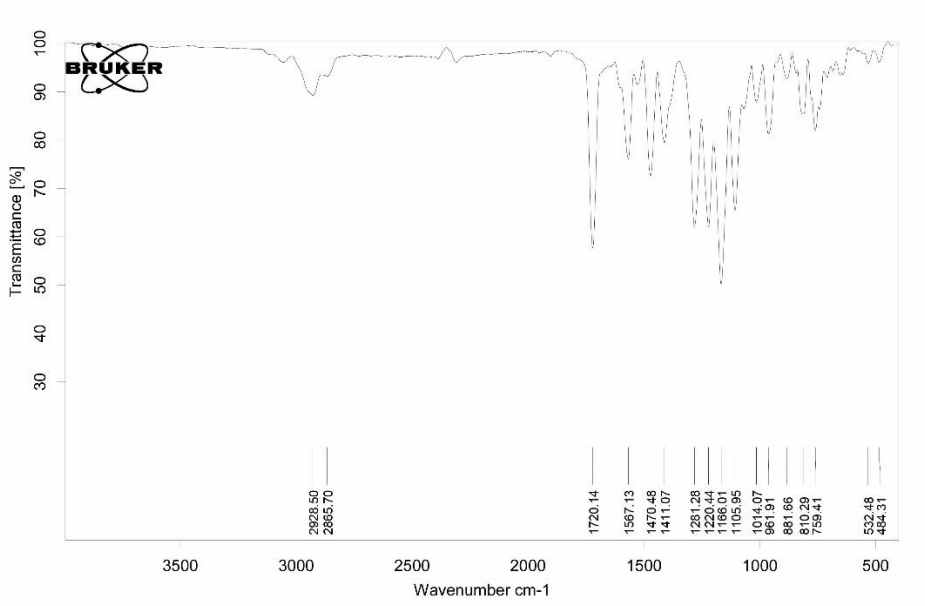

Figure 4: FTIR of Lisinopril

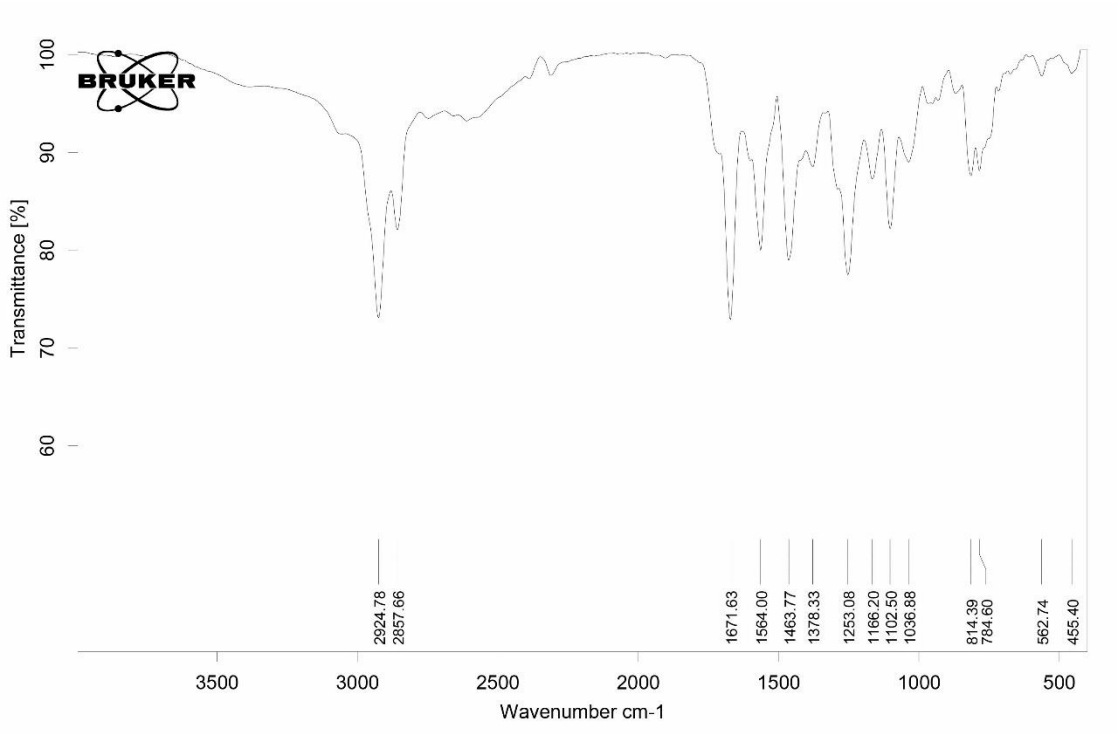

Figure 5 FTIR of Lisinopril with Sodium Starch Glycolate

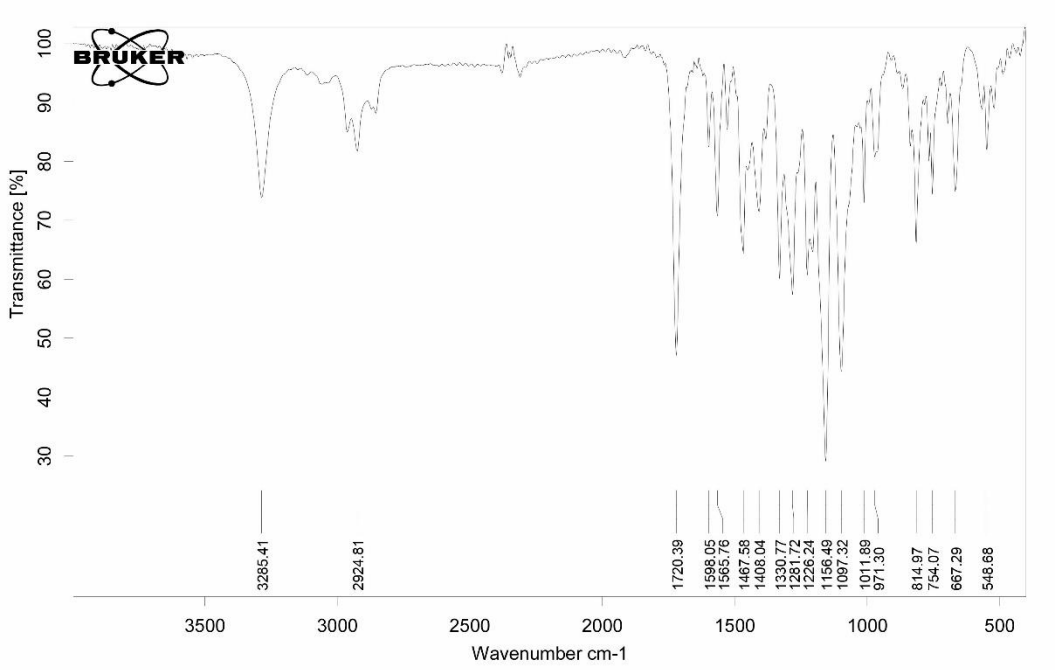

Figure 6 FTIR of Prepared Tablet

Characterization of prepared Lisinopril Tablet:

Table 9: Appearance of Lisinopril Tablet.

FORMULATION	APPEARANCE
F1-F6	Clear white, easily removed by die

Evaluation of Lisinopril Tablet:

Table 10. Precompression Evaluation of The Powder Blend

SR. NO.	PARAMETER	F1	F2	F3	F4	F5	F6
1.	Bulk density (g/cm^3)	**0.49**	**0.53**	**0.57**	**0.48**	**0.52**	**0.56**
2.	Tapped density (g/cm^3)	**0.60**	**0.66**	**0.70**	**0.59**	**0.64**	**0.69**
3.	Hausner's ratio	**1.2**	**1.2**	**1.2**	**1.2**	**1.2**	**1.2**
4.	Carr's index (%)	**12**	**15**	**18**	**10**	**13**	**16**
5.	Angle of repose (°)	**27**	**28**	**30**	**25**	**27**	**29**
6.	Flow rate (g/s)	**2.5**	**2.3**	**2.1**	**2.4**	**2.2**	**2.0**
7.	Compressibility index (%)	**12**	**14**	**16**	**11**	**13**	**15**
8.	Moisture content (%)	**0.8**	**0.7**	**0.9**	**1.0**	**0.8**	**0.6**
9.	Particle size distribution (%)	**90% passing 100 mesh**	**95% passing 100 mesh**	**90% passing 80 mesh**	**85% passing 100 mesh**	**90% passing 90 mesh**	**95% passing 80 mesh**

Bulk density

It has been stated that the bulk density values less than 1.2 g/cm2 indicate good packing and values greater than 1.5 g/cm2 indicate poor packing. The loose bulk density and tapped bulk density values for all the formulation varied in range of 0.312±0.12 g/cm3 to 0.321±0.27 g/cm3 respectively. The values obtained lies within the acceptable range.

Compressibility index

The percent compressibility of was determined by Carr's compressibility index, the results shown in Table 17. The percent compressibility for all formulation lies within the range of 5.12±0.29% to 10.33±0.51% indicates acceptable flow property.

Hausner ratio:

Hausner ratio was found to be in a range of 1.05±0.21 to1.11±0.37 which shows acceptable flow property and good packing ability.

Angle of repose:

The results of angle of repose of all the formulations were found to be in range of 250 16'±0.12 to 280 38'±0.15 indicating good flow property and this was further supported by lower compressibility index values. Thus, it can be concluded that the granules for all the batches possessed good flow characteristics.

Evaluation of Prepared tablet

Prepared tablet of all formulations (F1 to F8) were evaluated for different parameters such as thickness, hardness, weight variation, drug content and friability and results are shown in table no.

Table 11: Standard physical tests for Table

Parameter	F1	F2	F3	F4	F5	F6
Hardness (kg/cm2)	3.2±0.42	3.6±0.3	3.8±0.2	3.2±0.48	3.7±0.56	4.1±0.34
Thickness (mm)	3.9±0.2	3.9±0.2	3.5±0.2	3.6±0.2	3.6±0.2	3.8±0.2
Weight Variation (mg)	312.0±10	309.7±10	300.5±10	308.0±10	305.0±10	303.1±10
Friability (%)	0.45±0.18	0.81±0.2	0.35±0.2	0.65±0.37	0.12±0.67	0.38±0.62
Drug content (%)	96.18±0.12	93.18±0.54	98.54±0.19	92.18±0.34	94.18±0.69	98.21±0.37
Drug Release (%)	52±0.09	58±0.09	98±0.09	88±0.09	60±0.09	54±0.09

Hardness

Tablet hardness was determined by using Monsanto hardness tester. Hardness values of the formulation ranged from 3.2-4.1 kg/cm2, which indicate good strength of tablet

Friability Tablet

friability was determined by Roche friabilator and weight loss was calculated and represented in the terms of percent friability. Friability values of all the formulation were less than 1%, indicating good strength of tablet.

Weight variation

In weight variation test, the weight variation values of prepared Tablet between 299-309 mg. Pharmacopeial limit for percent of deviation for Tablet weighing is not more than 10 %. The average percent deviation of all Tablet was found to be within the limit and hence all formulation passes the weight variation test.

Thickness

Examination of Tablet from each batch showed flat circular shape with no cracks having white color. The thickness of Tablet was determined using Vernier caliper. The thickness of Tablet ranged from 3.6-3.9 mm. All formulations showed uniform thickness.

Content uniformity

The drug content was found to be uniform among all formulation and ranged from 92.18 -98.54%.

In-vitro drug release studies:

The study was carried out in modified dissolution apparatus with 900 ml of 0.1 N HCl as dissolution medium is taken in beaker and maintained at 37± 0.5 0C. The prepared tablets are placed in apparatus, at different time intervals 30 min. The samples were filtered through filter paper and analyzed for drug concentration after appropriate dilution at specific wavelength using UV-Visible spectrophotometer.

Table 12: In-vitro drug dissolution data of F1 to F3 formulation

FORMULATION	CUMULATIVE % DRUG RELEASE	TIME
F1	52	30
F2	58	30
F3	98	30

❖ All the values are representing as Mean ± S. D. (standard deviation) (n=3)

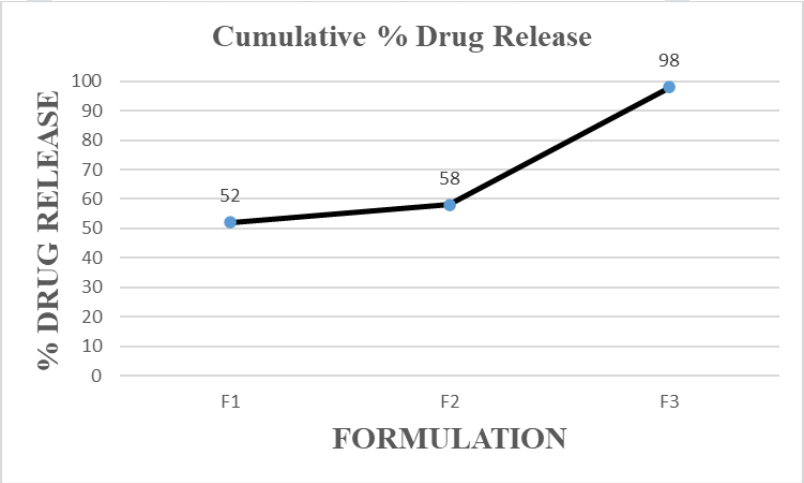

Figure 7 In-vitro dissolution profile of F1 to F3 formulation

Table 13: In-vitro drug dissolution data of F4 to F6 formulation

FORMULATION	CUMULATIVE % DRUG RELEASE	TIME
F4	88	30
F5	60	30
F6	54	30

❖ All the values are representing as Mean ± S. D. (standard deviation) (n=3)

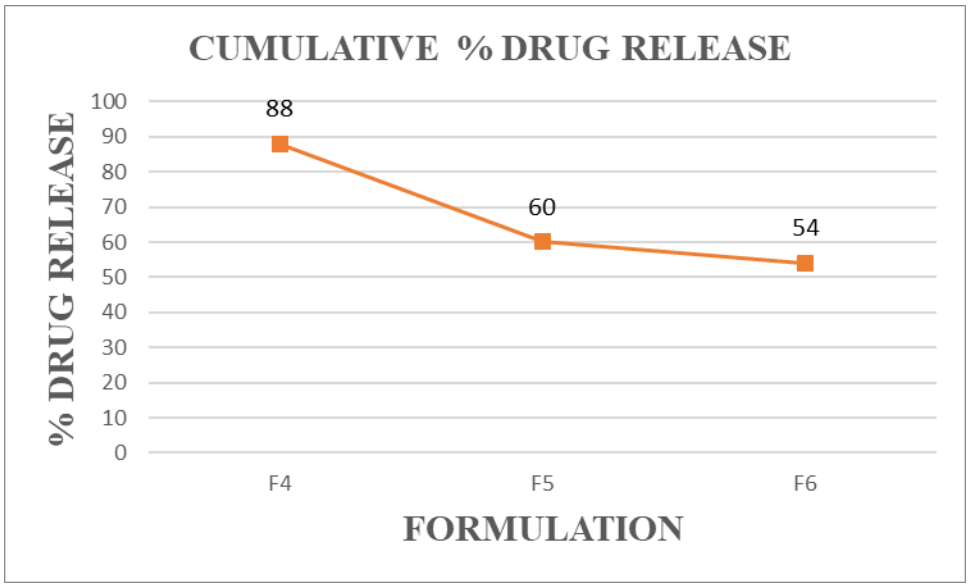

Figure 8 In-vitro dissolution profile of F4 to F6 formulation

All the formulation prepared were subjected to in-vitro release study. In vitro drug release profiles of all the formulations of Lisinopril prepared by wet granulation method was performed by modified dissolution apparatus. The temperature was maintained at 37± 0.5 0CThe % cumulative drug release graphs shown in figure (12- 13). When the Sodium Starch Glycolate add then increase in the drug release. But the color are buff and blackish. Because the amount of Colloidal silicon dioxide then the quantity of Colloidal silicon dioxide reduced in next prep. then the drug release are decreases. Then the Aerosil add to replace the Colloidal silicon then result are the clear white colour tablet and drug relase increases. In all these formulations F3 showed the drug release of 98.06 % within 30 min. it means that maximum drug release was observed using this formulation, so it is said to be optimized formulation of series is (F3) which is prepared by wet granulation method.

From the results (table 19-20 & figure 12-13)

Table 14: Parameters studied on F3 formulation before and after stability study

PARAMETER	BEFORE STABILITY TESTING	AFTER STABILITY TESTING
	F3	F3
Thickness	3.5±0.2	3.47±0.2
Hardness	3.8±0.2	3.8±0.2
Drug Content	98.54±0.19	98.48±0.21

Table 15: Cumulative percent drug released of optimized formulation before stability study after stability study

Time	Cumulative % Drug Release	
	Before Stability Study	After Stability Study
	F3	F3
30	98±0.09	97.86±14

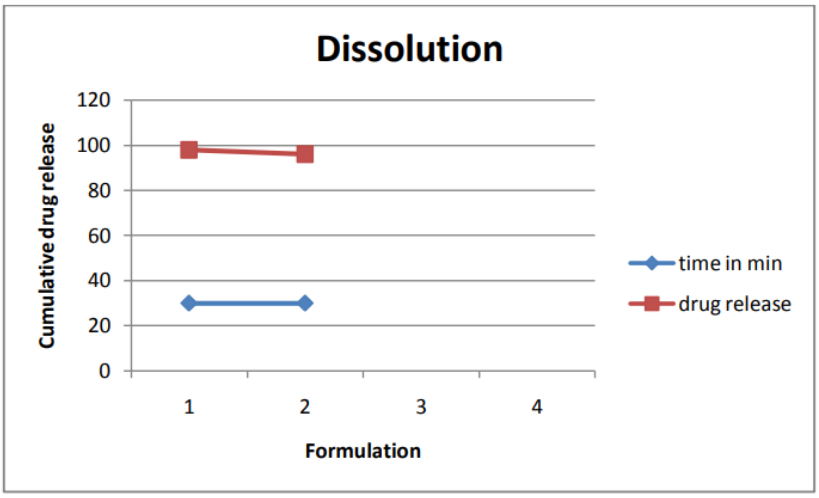

Figure No. 9: Dissolution profile of formulations F3 before stability & after stability study

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