Formulation And Evaluation of Lisinopril as Fast Dissolving Tablet

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Abstract-The objective of this research was to formulate fast dissolving tablets of Lisinopril that disintegrate in the oral cavity upon contact with saliva and there by improve therapeutic efficacy. Lisinopril is a drug widely used in the treatment of hypertension, congestive heart failure, heart attacks and in preventing renal and retinal complication of diabetes by inhibiting angiotensin converting enzyme (ACE). Fast dissolving tablets of Lisinopril were prepared by direct compression method comprising of three different super disintegrants-Sodium starch glycollate, Crosscarmellose sodium and Crosspovidone (4%, 7%, and 10%).

The prepared batches of tablets were evaluated for hardness, thickness, friability, weight variation, drug content, *in vitro* disintegration time, *in vitro* dispersion time, wetting time, water absorption ratio and *in vitro* dissolution studies. FTIR studies revealed that there was no chemical interaction between the drug and the excipients. Based on evaluating parameters, formulation prepared by using 10 % cross povidone was selected as the best formulation. Stability studies were carried out at 25^0C ± 20C / 60% ± 5% RH and 40^0C ± 20C / 75% ± 5% RH for formulation F9 for 60 days. The results of stability studies indicated no significant changes with respect to physicochemical properties, in vitro disintegration time, wetting time, and in vitro drug release.

Keywords: Fast dissolving tablets, Lisinopril, Superdisintegrant, Direct compression, Sodium starch glycollate, Crosscarmellose sodium, Crosspovidone

INTRODUCTION

Drugs are more frequently taken by oral administration. It is considered most natural, uncomplicated, convenient, safe means of administering drugs, greater flexibility in dosage form design, ease of production and low cost[1]. The most popular solid dosage forms being tablets and capsules; one important drawback of these dosage forms for some patients however is the difficulty to swallow[2].

In recent times many novel drug delivery systems (NDDS) have been formulated and studied, for improving safety, efficacy, and patient compliance. One of such NDDS which is of current interest is mouth dissolving tablets (MDT) or fast dissolving tablets (FDT). Fast dissolving tablets are defined as "The tablet drug delivery that disintegrates in oral cavity within a minute without the need for water or chewing"[3]. These tablets rapidly disperse when kept upon the tongue and instantaneously releases the drug. The drug could be absorbed from the mouth, pharynx and esophagus as the saliva passes into the stomach and hence may produce rapid onset of action[4]. MDT is also known as orally disintegrating tablet, fast dissolving tablet, fast-melting tablet, mouth melting tablet or fast-disintegrating tablet[5].

Ideal properties of fast dissolving tablet[6]:

- Require no water for oral administration, yet dissolve / disperse/ disintegrate in mouth in a matter of seconds.
- Have a pleasing mouth feel.
- Have an acceptable taste masking property.
- Be harder and less friable.
- Leave minimal or no residue in mouth after administration.

Disintegrants are agents added to tablet (and some encapsulated) formulations to promote the breakup of the tablet (and capsule "slugs") into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug substance. Super disintegrants are substances that are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. The task of developing rapidly disintegrating tablets is accomplished by using

suitable superintendents. Super disintegrants provide quick disintegration due to combined effect of swelling and water absorption.

Mechanism of superintendents:

1) Swelling: Particles swell and break up the matrix from within.
2) Porosity and capillary action (Wicking): Water is pulled into the pores by disintegrant and reduces the physical bonding forces between particles.
3) Due to disintegrating particle/particle repulsive forces: Water is drawn into the pores and particles repel each other because of resulting electrical force.
4) Due to deformation: Particles swell to precompression size on exposure to water and break up the matrix.

Lisinopril is an angiotensin converting enzyme (ACE) inhibitor having biological half-life approximately 25% but wide range of variation between individuals (6 to 60%). It does not undergo metabolism and is excreted unchanged entirely in the urine. Lisinopril absorption is not influenced by the presence of food in the gastrointestinal tract. After oral administration, peak serum concentration of Lisinopril occurs within 7 hrs. Lisinopril is a drug widely used in the treatment of hypertension, congestive heart failure, heart attacks and also in preventing renal and retinal complication of diabetes.

MATERIALS AND METHODS

Materials:

The materials which were used for the formulation were of pharma grade and were obtained as gift samples from different R&D centers. Lisinopril was procured from Jupiter Bioscience Ltd., Andhra Pradesh, India. Crosscarmellose sodium and microcrystalline cellulose were collected from Reliance Cellulose Products Ltd., Andhra Pradesh, India. Sodium starch glycollate was obtained from Maruti Chemicals, Gujarat, India. Cross povidone and aspartame was procured from Shreeji Chemicals, Mumbai, India. Mannitol was collected Moly Chem., Mumbai, India. Magnesium stearate and talc was obtained from S.D. Fine Chem. Ltd., Mumbai, India.

Methods:

Preformulation studies

Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms.

A) Organoleptic properties:

A small quantity of Lisinopril powder was taken on butter paper and its color, taste and odour was observed.

B) Solubility:

The solubility of Lisinopril in water, methanol and ethanol was determined.

C) Determination of melting point:

Melting point of the drug sample was determined by open capillary method.

D) Identification of pure drug:

Identification of Lisinopril was carried out by Infrared Absorption Spectroscopy.

E) Compatibility studies:

Compatibility of Lisinopril with super disintegrants was established by infrared spectral analysis. IR Spectral analysis was carried out to investigate the changes in chemical composition of the drug after combining it with the excipients.

Preparation of standard calibration curve of Lisinopril in phosphate buffer pH 6.8:

50 mg of Lisinopril dihydrate was accurately weighed in to 100 ml volumetric flask and volume made up with phosphate buffer pH 6.8 to give a concentration of 500µg/ml (Stock solution). From this stock solution aliquot with suitable dilutions were made in order to get concentration in between the Beer's range of 4-40 µg/ml. The absorbance was measured at 216 nm using UV Spectrophotometer. The standard curve was obtained by plotting absorbance v/s concentration in µg/ml.

PREPARATION OF LISINOPRIL FAST DISSOLVING TABLETS:

Accurate quantities of Lisinopril, super disintegrants (preferred super disintegrants in different concentrations), microcrystalline cellulose, Mannitol, aspartame, talc and magnesium stearate were weighed and passed through mesh #60. All the ingredients except lubricant were thoroughly blended in a glass mortar with pestle for 15 min. After sufficient mixing lubricant was added and mixed for additional 2 to 3

min. Before compression, hardness was adjusted. 10 mg of Lisinopril were compressed on 10-station rotary punching machine, each weighing 100 mg.

The composition of Lisinopril fast dissolving tablets were given in table no. 1.

EVALUATION OF FAST DISSOLVING TABLETS

A. Pre-compressional studies[7,8,9]:

a) Angle of Repose (Θ):

The angle of repose of API powder was determined by the funnel method. The accurately weighed powder blend was taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

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

Where, Θ is the angle of repose, h is the height of pile and r is the radius of the base of pile.

b) Bulk Density and Tapped density:

Loose bulk density (LBD) and tapped bulk density (TBD) of tablet blends were determined using bulk density apparatus. Tablet blend was passed through #18 sieve to break the clumps and transferred to 100ml graduated cylinder. Initial volume was observed. The cylinder was tapped initially 200 times from a distance of 14 ± 2 mm. The tapped volume was measured to the nearest graduated unit. The LBD and TBD were calculated in g/ml using formula:

LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

c) Hausner ratio:

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. The hausner ratio of the powder was determined by the following equation:

$$\text{Hausner ratio} = \text{TBD} / \text{LBD}$$

Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

d) Carr's Index:

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it is packed down. The formula for Carr's Index is as below

$$\text{Carr's Index (\%)} = [(\text{TBD}-\text{LBD}) \times 100]/\text{TBD}$$

Where,

LBD = Loose Bulk Density

TBD = Tapped Bulk Density

B. Post-compressional studies:

a) General appearance:

The fast dissolving tablets, morphological characterization which includes size, shape, colour, presence or absence of odour, taste surface texture was determined.

b) Thickness[10]:

Three tablets were picked from each formulation randomly and thickness was measured individually. The tablet thickness was measured using vernier caliper.

c) Hardness[10]:

The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2.

d) Friability test[11]:

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche Friabilator was used for the purpose. Pre-weighed sample of ten tablets were placed in the Friabilator, which was then operated at 25 rpm for 4 minutes or ran upto 100 revolutions. After 100 revolutions the tablets were dusted and reweighed. Compressed tablets should not loose more than 1% of their weight.

The % friability was then calculated by the following formula:

Percentage friability = (Initial weight - Final weight /Initial weight) × 100

e) Weight variation[10]:

20 tablets were selected randomly from each formulation and weighed individually to check for weight variation. The US Pharmacopoeia allows a little variation in the weight of a tablet. In all the formulations the tablet weight was 100 mg, hence 10% weight variation was allowed.

f) Drug content uniformity:

Two tablets were weighed and powdered. Powder equivalent to 10 mg drug was transferred into a 100 ml volumetric flask. Volume was made with buffer pH 6.8. After few minutes the solution was filtered; rejecting first few ml of the filtrate. 10ml of filtrate was taken in a 50 ml volumetric flask and diluted up to the mark with buffer pH 6.8 and analyzed spectrophotometrically at 216 nm. The concentration

of Lisinopril (in µg/ml) was calculated by using the standard calibration curve of Lisinopril.

g) Wetting time and water absorption ratio[12]:

A piece of tissue paper folded twice was placed in a small petridish (i.d = 6.5 cm) containing 6 ml of water. A tablet was placed on the paper and the time required for complete wetting was then measured.

The water absorption ratio, R, was determined using the following equation,

$R = Wa - Wb / Wb \times 100$

Where,

Wb is the weight of the tablet before water absorption and

Wa is the weight of the tablet after water absorption.

h) *In vitro* dispersion time[13]:

One tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffers at 37 ± 0.5ºC and the time required for complete dispersion was determined.

i) *In vitro* disintegration time[14]:

In vitro disintegration time was performed by apparatus specified in USP at 50 rpm. Phosphate buffer pH 6.8, 900 ml was used as disintegration medium, and the temperature of which was maintained at 37 ± 2°C and the time in second taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

j) *In vitro* drug release studies:

In vitro drug release studies were carried out using dissolution apparatus USP type XXIII at 50 rpm. The dissolution medium consisted of 500 ml of phosphate buffer pH 6.8 maintained at 37 ± 1^0C. The drug release at different time intervals was measured using a double beam UV Spectrophotometer at 216 nm.

k) Data Analysis:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, Korsmeyer-Peppas release model and Hixson-Crowell equation.

l) Stability Studies:

Stability studies were carried out at 25^0C ± 2^0C / 60% ± 5% RH and 40^0C ± 2^0C / 75% ± 5% RH for a period of 60 days for the selected formulation. The formulation was then evaluated for changes in the physicochemical properties, wetting time, *in vitro* disintegration time and *in vitro* drug release.

RESULTS AND DISCUSSION

The present study was to formulate fast dissolving tablets of Lisinopril using superdisintegrants (sodium starch glycollate, crosscarmellose sodium and crosspovidone) in different concentrations by direct compression method. The prepared tablets were evaluated for physiochemical properties, wetting time, water absorption ratio, *in vitro* dispersion time, *in vitro* disintegration time, *in vitro* dissolution studies and stability studies.

Preformulation studies:

Lisinopril was found to be soluble in water, sparingly soluble in methanol and practically insoluble in ethanol. Lisinopril melting point was reported within the range of 159°C to 161°C. The IR spectra of pure drug complied with the reference standard IR spectrum of Lisinopril shown in figure no. 1. Physical mixture of Lisinopril and formulative ingredients were subjected for IR spectroscopy which indicated that the drug was compatible with the excipients. The FTIR spectra of physical mixture were shown in figure no. 2, 3, and 4.

Precompression parameter:

Blended drug/excipient mixture of all the formulations were subjected for various precompressional evaluation parameters such as bulk density, tapped density, compressibility index, hausner's ratio and angle of repose who's values were in the range of 0.46 to 0.55 gm/cc, 0.52 to 0.64 gm/cc, 11.11 to 14.75%, 1.12 to 1.17 and 20 to 25° respectively. All the nine batches showed good passable compressibility index and excellent angle of repose. These values were within limit and had favorable flow properties for compression, reported in table no. 2.

Post compression study:

Tablets of all formulations (F1 to F9) were evaluated for different parameters such as thickness, hardness, weight variation, drug content and friability showed in table no. 3. Physical evaluation of tablets for all batches showed tablets were flat, white in color, circular in shape and having good physical appearance. The thickness of tablets ranged from 2.701 mm to 2.714 mm. Hardness of all formulations was found to be within 3.5 to 3.8 kg/cm^2. In weight variation test, the Pharmacopoeia limit for percent of deviation for tablets having weight 100mg was ±10%. The average percent deviation of all formulations was found to be within the limit. The drug content was

found to be uniform among all formulation and ranged from 97.58% to 99.47%. The friability of tablets of all formulations ranged from 0.24 to 0.39%. The *in vitro* disintegration time was less than 40 seconds and *in vitro* dispersion time was less than 54 seconds. The *in vitro* disintegration time and *in vitro* dispersion time for all nine formulations were given in table no. 4. The wetting time was found to be less than 45 seconds and the water absorption ratio were found to be in the range of 57.17 to 72.83 which were given in table no. 5. Comparison between *in vitro* disintegration time and wetting time of formulated Lisinopril fast dissolving tablets was shown in figure no. 5.

The *in-vitro* dissolution data of formulation were shown in table no. 6, 7 and 8 and figure no. 6, 7 and 8. Formulation F1, F2 and F3 released 89.11 %, 92.56 %, 93.76 % drug respectively in 15 mins. Formulation F4, F5 and F6 released 90.01 %, 92.17 %, 96.34 % drug respectively in 15 mins. Formulation F7, F8 and F9 released 92.97 %, 95.84 % and 98.97 % drug respectively in 15 mins. *In vitro* dissolution studies revealed that the release rate of Lisinopril from fast dissolving tablet containing Crosspovidone (F9) was maximum i.e 98.97%.

Stability studies were conducted for formulations F9 at $25^0C \pm 2^0C$ / 60% ± 5% RH and $40^0C \pm 2^0C$ / 75% ± 5% RH for 60 days. Formulation F9 was found to be stable and there were no significant changes with respect to physicochemical properties, *in vitro* disintegration time, wetting time and *in vitro* drug release.

CONCLUSION

The present investigation deals with the development of Lisinopril fast dissolving tablets leading to an increase in bioavailability of the drug, quick onset of pharmacological action and increase in patient compliance due to ease of administration. From the results obtained, it can be concluded that FTIR studies concluded that drug and excipients were compatible with each other. The formulated tablets were satisfactory in terms of hardness, thickness, friability, weight variation, drug content, wetting time, water absorption ratio, *in vitro* disintegration time, *in vitro* dispersion time and *in vitro* drug release. Formulation F9 containing Superdisintegrant Crosspovidone showed least wetting time and highest *in vitro* drug release. Formulation F9 was found to be the best based on *in vitro* drug release, wetting time and *in vitro* disintegration time. Data obtained from kinetic study revealed that best formulation F9 followed Hixson Crowell release. The stability studies conducted on formulation F9 revealed that there were no significant changes when tablets were stored at $25^0C \pm 2^0C$ / 60% ± 5% RH and $40^0C \pm 2^0C$ / 75% ± 5% RH for 60 days.

ACKNOWLEDGEMENT

Authors thanks to, Ezhuthachan College of Pharmaceutical Sciences for providing necessary facilities for conducting the present work.

Table no. 1: Composition of fast dissolving tablets of Lisinopril

INGREDIENTS	FORMULATIONS								
	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Lisinopril	10	10	10	10	10	10	10	10	10
Sodium Starch Glycollate	4	7	10	-	-	-	-	-	-
Crosscarmellose Sodium	-	-	-	4	7	10	-	-	-
Crosspovidone	-	-	-	-	-	-	4	7	10
Microcrystalline Cellulose	46	43	40	46	43	40	46	43	40
Mannitol	35	35	35	35	35	35	35	35	35
Aspartame	2	2	2	2	2	2	2	2	2
Magnesium Stearate	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2
Total weight	100	100	100	100	100	100	100	100	100

Table no. 2: Pre compression evaluation of drug/excipients mixture

Formulation code	Angle of Repose	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Carr's Index %	Hausner Ratio
F1	22.95	0.49	0.56	12.50	1.14
F2	22.09	0.47	0.53	11.32	1.12
F3	23.21	0.55	0.64	14.06	1.16
F4	22.88	0.46	0.52	11.53	1.13
F5	21.34	0.47	0.54	12.96	1.14
F6	20.13	0.55	0.62	11.29	1.12
F7	21.29	0.48	0.54	11.11	1.12
F8	20.59	0.47	0.53	11.32	1.12
F9	24.01	0.52	0.61	14.75	1.17

Table no. 3: Post compression evaluation parameters of formulated Lisinopril fast dissolving tablets

Formulation Code	Thickness (mm) (n=3)	Hardness (kg/cm^2) (n=3)	Friability (%) (n=10)	Weight variation test (mg) (n=20)	Drug Content (%) (n=3)
F1	2.703 ± 0.01	3.5 ± 0.24	0.37	101.00 ± 1.01	98.70 ± 0.73
F2	2.711 ± 0.04	3.8 ± 0.25	0.33	103.55 ± 1.11	98.55 ± 1.09
F3	2.705 ± 0.01	3.6 ± 0.27	0.39	100.30 ± 1.12	99.30 ± 0.56
F4	2.709 ± 0.03	3.5 ± 0.23	0.24	102.55 ± 1.17	98.90 ± 1.28
F5	2.714 ± 0.06	3.7± 0.25	0.27	101.00 ± 1.05	98.65 ± 1.51
F6	2.701 ± 0.03	3.6 ± 0.26	0.34	99.80 ± 0.11	97.58 ± 0.44
F7	2.704 ± 0.02	3.5 ± 0.24	0.29	102.25 ± 1.22	98.29 ± 0.75
F8	2.711 ± 0.01	3.8 ± 0.23	0.35	100.05 ± 1.15	97.90 ± 0.65
F9	2.712 ± 0.04	3.7 ± 0.24	0.32	101.05 ± 1.77	99.47 ± 0.47

Table no. 4: Wetting time and water absorption ratio of formulated Lisinopril fast dissolving tablet

Formulation Code	Wetting time (sec)	Water Absorption Ratio
F1	44 ± 1.23	57.17 ± 0.24
F2	42 ± 1.07	59.23 ± 0.32
F3	40 ± 1.03	62.13 ± 1.17
F4	41 ± 1.30	59.98 ± 0.89
F5	37 ± 1.13	62.81 ± 0.57
F6	36 ± 1.15	66.43 ± 0.42
F7	36 ± 1.17	65.13 ± 0.12
F8	32 ± 1.06	69.03 ± 0.85
F9	29 ± 1.04	72.83 ± 0.91

Table no. 5: *In vitro* disintegration time and *in vitro* dispersion time of Lisinopril fast dissolving tablet

Formulation Code	*In vitro* Disintegration Time (sec)	*In vitro* Dispersion Time (sec)
F1	39 ± 0.86	53 ± 0.81
F2	35 ± 0.40	50 ± 0.80
F3	32 ± 0.50	49 ± 0.96
F4	34 ± 0.49	49 ± 0.41
F5	30 ± 0.22	45 ± 0.35
F6	27 ± 0.31	42 ± 0.30
F7	25 ± 0.44	37 ± 1.40

F8	23 ± 0.24	33 ± 0.65
F9	20 ± 0.36	31 ± 0.45

Table no. 6: Cumulative % Drug released for formulated Lisinopril fast dissolving tablets containing SSG (F1- F3)

Sr. No.	Time (min)	% Cumulative drug release		
		F1	F2	F3
1.	0	0	0	0
2.	3	49.64	55.95	60.28
3.	6	58.05	70.66	73.75
4.	9	69.55	82.26	84.39
5.	12	78.36	88.61	89.22
6.	15	89.11	92.56	93.76

Table no. 7: Cumulative % Drug released from formulated Lisinopril fast dissolving tablets containing CCS (F4- F6)

Sr. No.	Time (min)	% Cumulative drug release		
		F4	F5	F6
1.	0	0	0	0
2.	3	60.52	63.26	65.61
3.	6	71.96	73.61	77.14
4.	9	79.46	81.11	85.41
5.	12	86.16	88.84	92.51
6.	15	90.01	92.17	96.34

Table no. 8: Cumulative % Drug released from formulated Lisinopril fast dissolving tablets containing CP (F7- F9)

Sr. No.	Time (min)	% Cumulative drug release		
		F7	F8	F9
1.	0	0	0	0
2.	3	65.34	68.52	70.52
3.	6	74.26	78.47	82.03
4.	9	82.40	86.85	89.23
5.	12	89.57	92.27	96.41
6.	15	92.97	95.84	98.97

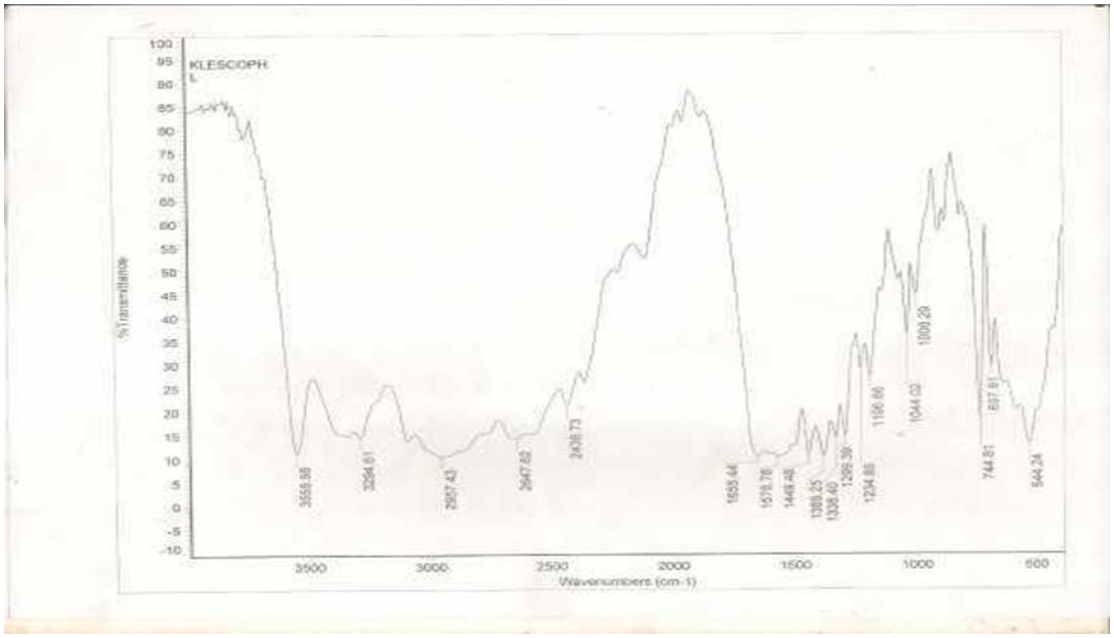

Figure no. 1: FTIR spectra of Lisinopril pure drug

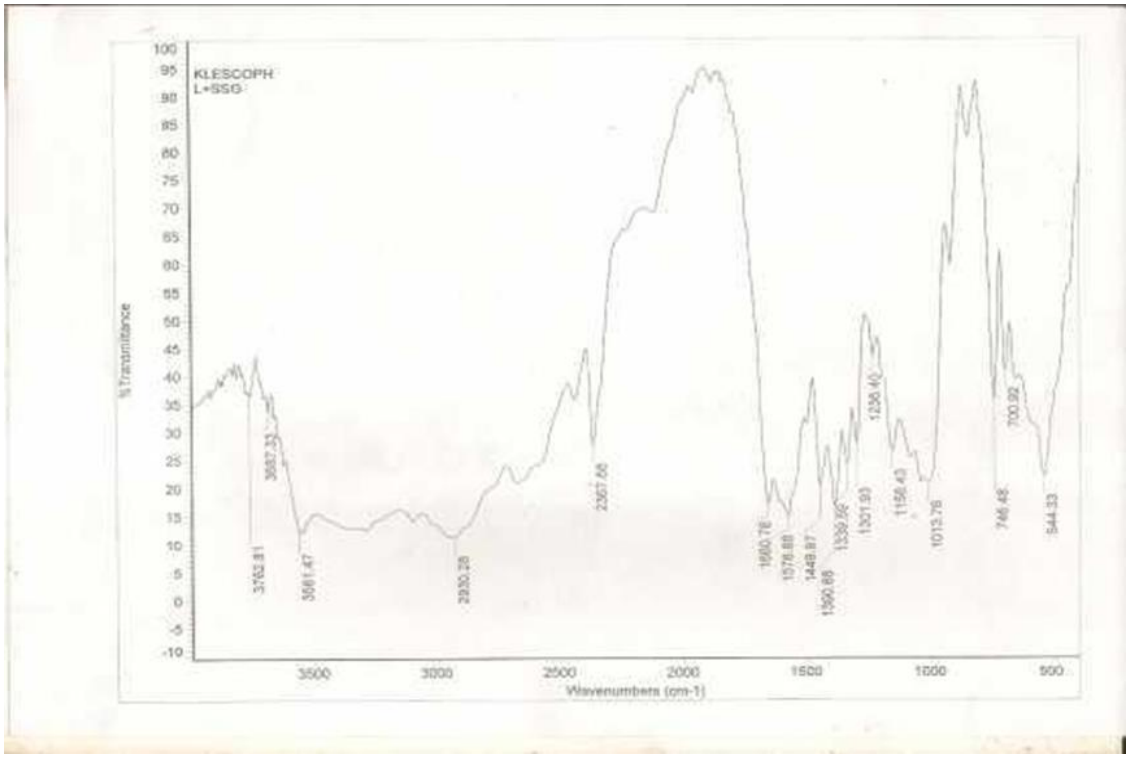

Figure no. 2: FT-IR Spectra of Physical mixture of Lisinopril + SSG

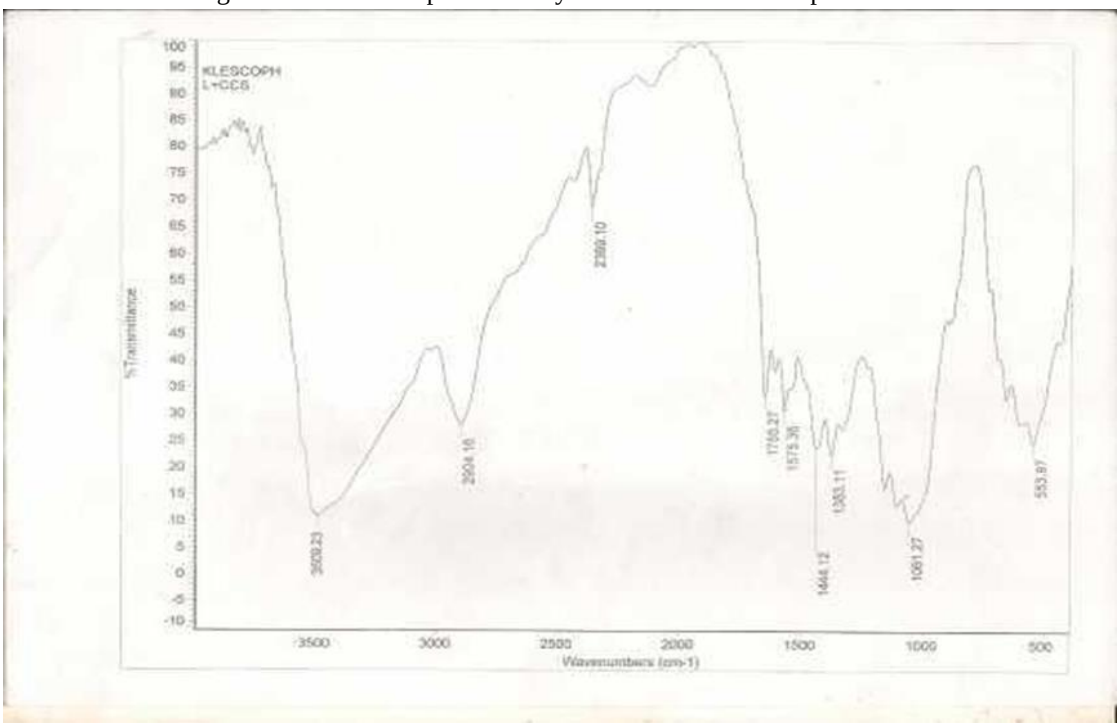

Figure no. 3: FT-IR Spectra of Physical mixture of Lisinopril + CCS

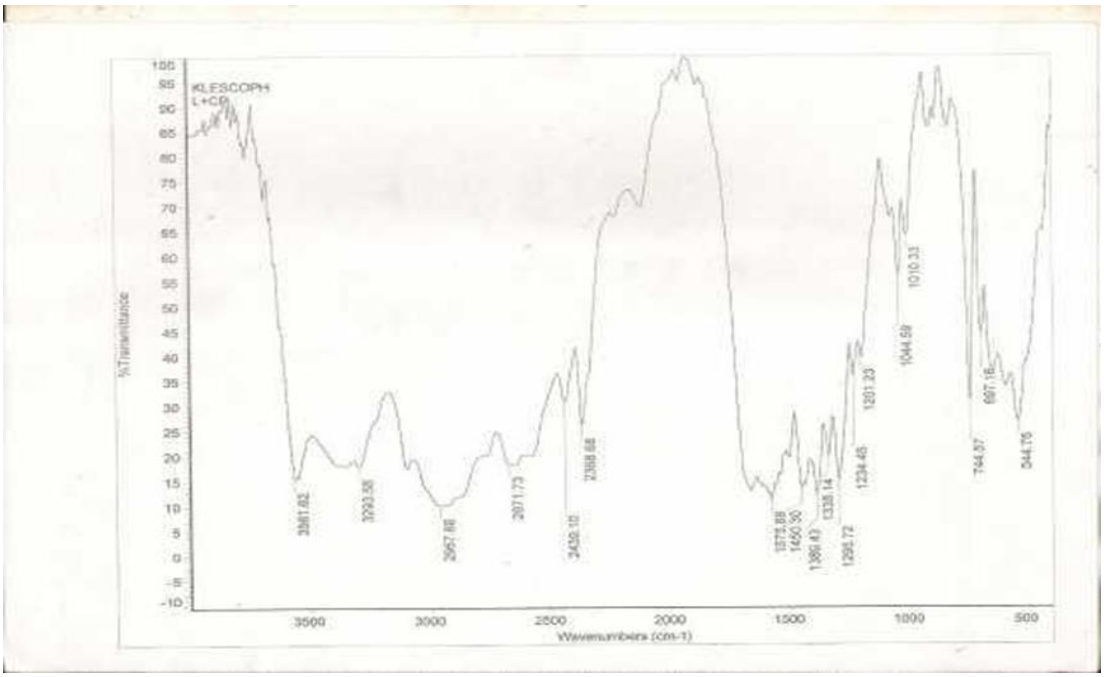

Figure no. 4: FT-IR Spectra of Physical mixture of Lisinopril + CP

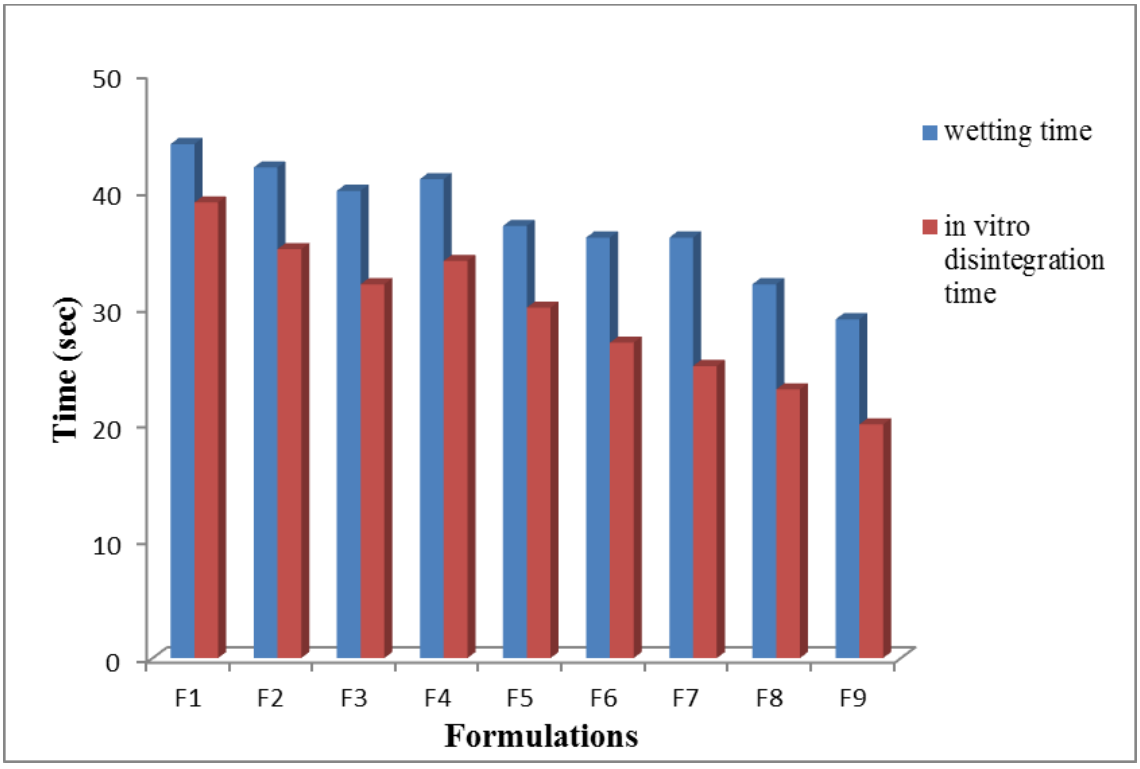

Figure no. 5: Comparison between *in vitro* disintegration time and wetting time of formulated Lisinopril fast dissolving tablets

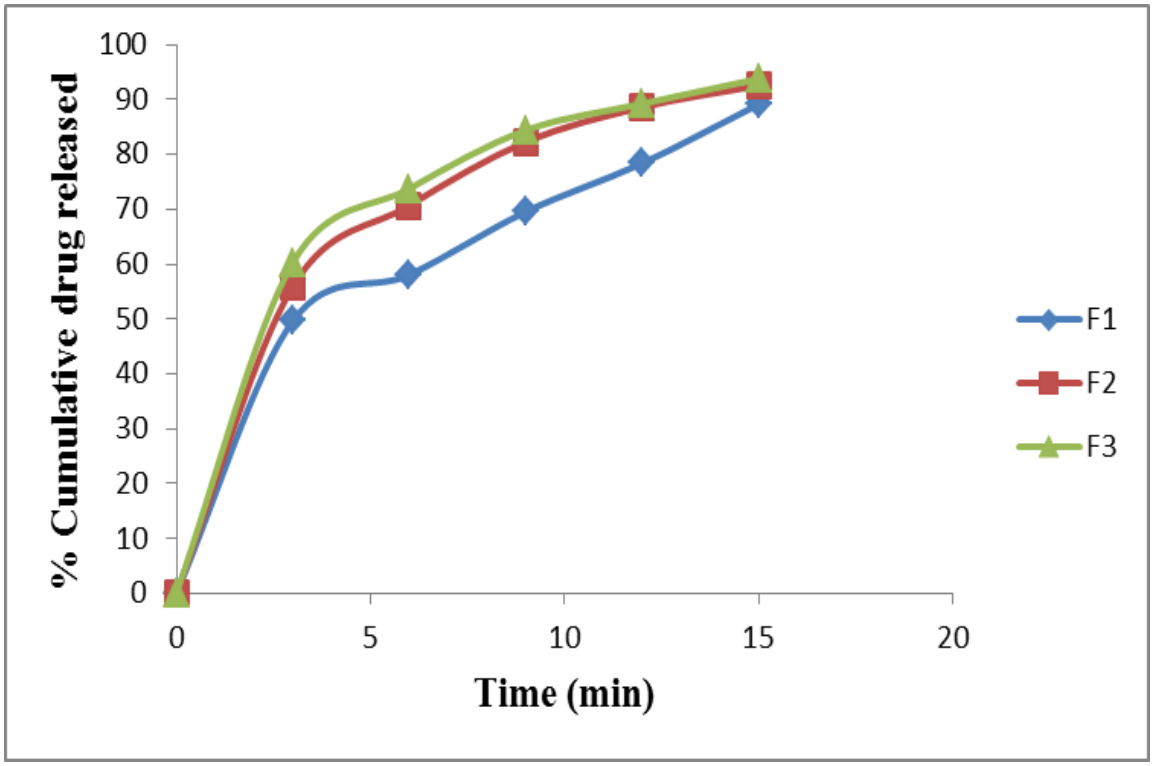

Figure no. 6: Plots of cumulative % drug released as a function of time for formulated Lisinopril fast dissolving tablets containing SSG (F1-F3)

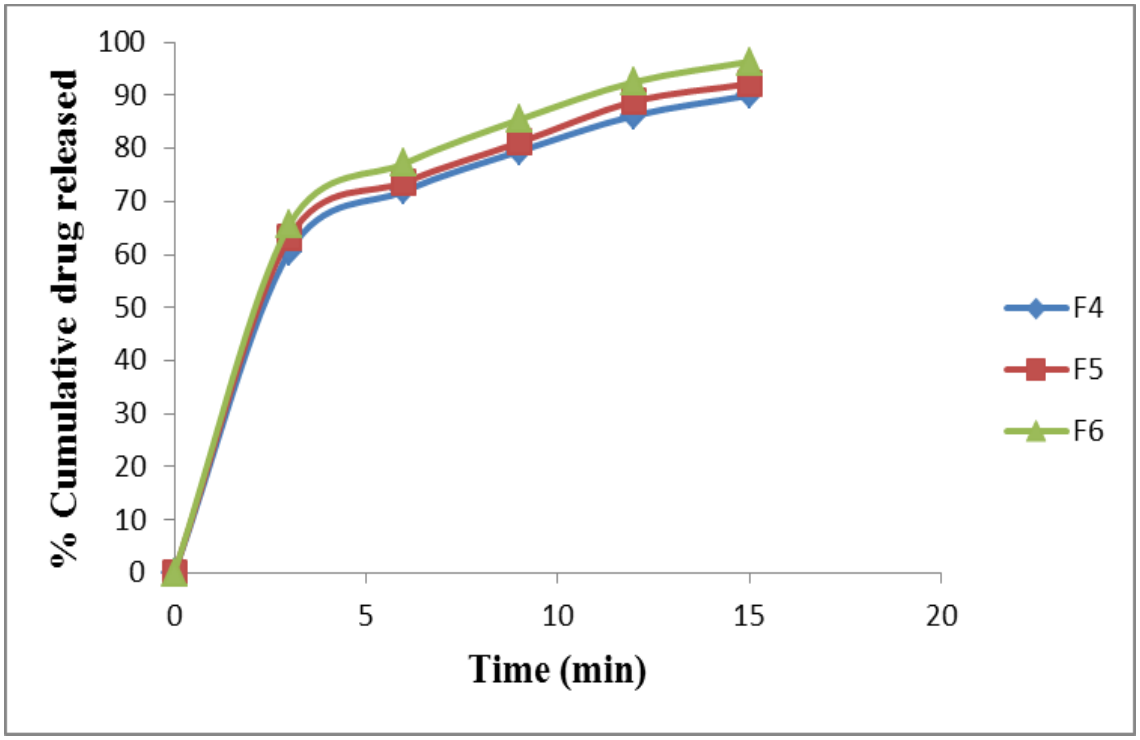

Figure no. 7: Plots of cumulative % drug released as a function of time for formulated Lisinopril fast dissolving tablets containing CCS (F4-F6)

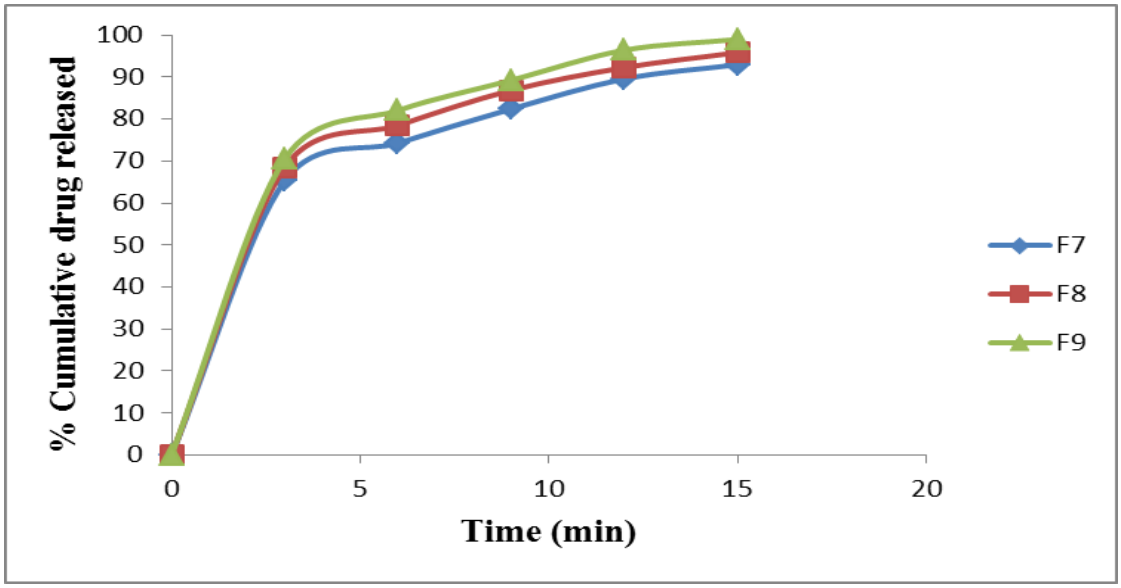

Figure no. 8: Plots of cumulative % drug released as a function of time for formulated Lisinopril fast dissolving tablets containing CP (F7-F9)

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