Formulation and Evaluation of Lisinopril Fast Disintegrating Films and Tablets

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ABSTRACT:

Lisinopril is an angiotensin converting enzyme inhibitor used in the management of hypertension with low bioavailability. The objective of the study is to formulate oral disintegrating tablets (ODT) and oral disintegrating films (ODF) of Lisinopril, to improve the versatility, patient compliance, accurate dosing and to resolve the swallowing problems in geriatric patients. Present study involves the comparision between the ODT and ODF of lisinoprilthat disintegrate or disperse in the saliva within a few seconds.ODF were prepared by solvent casting method using film forming polymers like HPMC E15, 5cps, 50cps in different ratios & prepared batches of films were evaluated for the drug content, film thickness, disintegration time and *in vitro* drug release. Among all ODFs, the formulation A3 containing HPMC E15 (drug: polymer ratio = 1:2) was found to be the best formulation which releases 99.59±0.32% of the drug within 15 min and with a disintegration time of 22.39sec. ODTs were prepared by direct compression method using different concentrations of super-disintegrants. Among all ODTs, the formulation F15 containing CP5% + CCS5% was considered to be the best formulation, which releases up to 99.87% of the drug in 25 min with a disintegration time 17.66 sec. Based on the results, ODTs were found to have faster disintegration time and drug release than ODFs.

Key words: Sodiumstarch glycollate, Croscarmellose sodium, Crosspovidone, Oral disintegration tablets, Oral disintegration films, Lisinopril.

Abbreviations:

ODF - Oral Disintegrating Films, ODT - Oral Disintegrating Tablets, HPMC – Hydroxy propyl methyl cellulose, Cps - Centipoise, mm - millimeter, nm - nanometer, cm -centimeter, C - Centigrade

Introduction

Major portion of the world population constitutes of the elderly [1]. A majority of elderly patients complain of a decline in swallowing ability with their age. This hinders administration of some dosage forms such as tablets, capsules or powders etc [2].

Oral disintegrating dosage forms have become a prominent new drug delivery system. These dosage forms disintegrate in the oral cavity within fraction of a second andcan be taken without water or chewing .These dosage forms help in improving the patient compliance and hence can be useful for pediatric, geriatric and also dysphagia patients. They are also suitable for the mentally ill, bedridden and for the

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patients who do not have easy access to water [3, 4].

Oral dosing remains the preferred mode of administration for many types of medication due to its simplicity, versatility, convenience, and patient acceptability. The technologies utilized for fabrication of oral disintegrating tablets are Zydis, Lyoc, Orasolv, Durasolv, Wowtab, Flashtab, Frosta, Advatab [5-8]. The technologies utilized for fabrication of oral disintegrating films are Quickdis, Soluleaves, Wafertab, Foamburst, X gel [9]. The techniques for preparation are commonly based on swelling, wicking of water, porosity etc [10].

Fast disintegrating films can be formulated using film forming polymers [11]. All excipients used in the formulation of ODFs should be approved for use in oral pharmaceutical dosage forms and should be Generally Regarded as Safe according to the regulatory perspectives. It is necessary to use suitable excipients with good compatability and disintegrating ability in order to develop a rapidly disintegrating tablet with direct-compression method. Several factors must be considered while selecting a super disintegrant, as its concentration effects most of the factors like disintegration time, hardness etc. The superdisintegrant primarily effect the rate of disintegration but when used at high levels, it can also affect mouth feel, tablet hardness, and friability. The key factor for the rapid disintegration of a tablet is its ability to swell. A 'disintegrating agent' has a high swelling (or disintegrating) force and a 'swelling agent' has a low swelling force.

Suitability of Lisinopril for this investigation:

Lisinopril is an anti hypertensive agent, with a molecular weight of 405.488g/mol, with an initial dose of 2.5mg once a day, soluble in water [12]. Till now there are no reports regarding the comparative study of Lisinopril ODT and ODF.

Advantages of Lisinopril as ODT and ODF:

ODT and ODF facilitates patient administration more than conventional tablets or capsules in case of chronic medication as in hypertension. Hence, in the present study ODT and ODF of Lisinopril which is an anti-hypertensive agent, were formulated in order to resolve the swallowing problems in geriatric patients with hypertension. These can be administered as such by the patient, without the need of water also.

Super-disintegrants commonly used are Crosspovidone, Sodium starch glycollate and Croscarmellose sodium. The mechanism of Crosspovidone is mainly depending on capillary action and for Sodium starch glycollate and Croscarmellose sodium is mainly depending on high swelling action [13, 14]. In the present study, fast disintegrating tablets were developed by using single and a combination of different super-disintegrants. The effect on disintegration time by using both capillary and high swelling mechanisms in a formulation was studied

Materials and methods

Materials

Lisinopril, Crosspovidone, Croscarmellose sodium, Sodium starch glycollate, Avicel pH 102, Sodium stearyl fumerate, Pearlitol SD 200 (D-Mannitol) and Sodium saccharin were gift samples from Hetero Drugs, Hyderabad, India. Orange flavor and Methanol were obtained from Finar chemicals limited, Ahmedabad, India. Potassium dihydrogen orthophosphate purified obtianed from SD Fine chemicals limited, Mumbai, India. Polyethlene glycol 400 (plasticizer) was obtained from SD Fine chemicals limited, Mumbai, India. Eosin (dye) was obtained from Selkrom, Mumbai, India.

Methods

Preparation of fast disintegrating film

An aqueous solution of HPMC (E15, 5cps or 50 cps) was prepared in distilled water, and Lisinopril was added to this aqueous polymeric solution. This step was followed by the addition of plasticizer such as polyethylene glycol (PEG 400), sweetener i.e sodium saccharin and a suitable flavor. The solution was cast on petriplate with an area of 40cm^2 and dried at room temperature (28-30°C) for one day. The film was carefully removed from the petriplate, checked for the imperfections and cut to the

required size ($2\times2cm^2$) to deliver the equivalent dose per strip. Film samples with air bubbles, cuts or imperfections were excluded from the study.

Preparation of fast disintegrating tablet

All the required ingredients were weighed accurately and passed through 40 mesh to get uniform sized particles. Whole amount of drug, pearlitol SD 200, Avicel pH 102, sodium saccharine and flavour except lubricant were mixed in the increasing order of their weights in a mortar. To this mixture, talc and sodium stearyl fumerate were added. The final mixture was shaken manually for 5-10 minutes in a plastic bag. This powder was passed through the hopper of 16 station rotary tabletting machine and punched into tablets using 5mm s/c. The process is similar for all the formulations, which were prepared by direct compression technique.

Evaluation of films

Thickness

The thickness of the film ($5 \times 2cm^2$) was measured at four different points on one film using screw gauge. For each formulation ten selected films were used and average thickness was recorded [15].

Weight variation test

Twenty films were randomly selected from each formulation and their average weight was calculated using digital balance. Individual weight of each film was also noted using the same and compared with the average weight.

Content uniformity test

The formulated polymeric films were assayed for drug content in each case. Three polymeric films from each formulation were assayed for content of drug. Films from each formulation were taken, and were allowed to dissolve in 100 ml phosphate buffer pH 6.8 on a rotary shaker. The solution was diluted suitably and the absorbance of the solution was measured using UV-Visible spectrophotometer at a wavelength of 218nm against phosphate buffer pH6.8 as blank [15-17].

Evaluation of Tablets

Pre compression parameters:

Preformulation study

It is the first step in rational development of dosage forms of drug substance. Pre formulation testing is defined as investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It gives information needed to define the nature of the drug substance and provide frame work for the drug combination with pharmaceutical excipients in the dosage form. This include:

Bulk Density (Db)

It is the ratio of total mass of powder to the bulk volume of powder [18]. It was measured by pouring a weighed quantity of powder (passed through standard sieve # 20) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$\mathbf{D_b = M/ V_b}$$

Where,

M is the mass of powder

V_b is the bulk volume of the powder.

Tapped Density (D_t)

It is the ratio of total mass of the powder to the tapped volume of the powder [18]. Volume was measured by tapping the powder for 750 times and the tapped volume was noted, if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and then the tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2% (in a bulk density apparatus). It is expressed in g/ml and is given by

$$\mathbf{D_t = M/ V_t}$$

Where,

M is the mass of powder

V_t is the tapped volume of the powder.

Carr's index (or) % compressibility

It indicates powder flow properties [17]. It is expressed in percentage and is given by

$$I = \frac{Dt - Db}{Dt} \times 100$$

Where,

D_t is the tapped density of the powder and

D_b is the bulk density of the powder.

Hausner ratio

Hausner ratio is an indirect index of ease of powder flow (18). It is calculated by the following formula:

Hausner ratio = D_t/D_b

Where,

Dt is the tapped density.

Db is the bulk density.

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

Angle of Repose

The friction forces in a loose powder can be measured by the angle of repose (θ) [18]. It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane

This can be calculated by:

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

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

Where, θ is the angle of repose.

h is the height in cms

r is the radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property is inverse.

Post compression parameters [19-21]

Weight variation test

Twenty tablets were randomly selected from each formulation and their average weight was calculated using digital balance, then the standard deviation was calculated by comparing the individual weight with the average weight. The Mean ± S.D was noted. The tablets meet USP specifications if not more than 2 tablets lie outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Thickness measurement

Randomly 10 tablets were taken from each formulation and their thickness was measured using a screw gauge. The tablet was placed between two anvils of the screw guage and sliding knob was rotated until the tablet was tightly fitted, then the reading was taken. The average thickness and the standard deviation was calculated and then, Mean ± S.D was noted. The tablet thickness should be controlled within a ± 5% variation of the standard value.

Hardness and Friability

The tablet hardness of different formulations was measured using the Monsanto hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet, and a zero was taken. The upper plunger was then forced against the spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is recorded, and the zero force reading is deducted from it. Generally, a minimum hardness of 4 kg is considered acceptable for uncoated tablets. The hardness for ODTs should be preferably 3 kg [19-21].

Method (Friability)

This test was performed using a laboratory friability tester known as Roche Friabilator. 10 tablets were weighed and placed in a plastic chambered friabilator attached to a motor, which revolves at a speed of 25 rpm, dropping the

tablets from a distance of 6 inches with each revolution. The tablets were subjected to 100 revolutions for 4 minutes. After the process, these tablets were dedusted and reweighed. Percentage loss of tablet weight was calculated.

$$\% \text{ Friability} = \frac{(w1-w2)}{w1} \times 100$$

Where,

W1 = Initial weight of the 20 tablets before testing.

W2 = Final weight of the 20 tablets after testing.

Friability values below 1% are generally acceptable.

Assay

Twenty tablets were randomly selected, weighed and finely powdered and quantity of powder equivalent to one tablet was added to 100 ml solvent i.e. pH 6.8 phosphate buffer and in a conical flask. Conical flask was placed on a rotary shaker overnight. An aliquot of solution was centrifuged and supernatant was filtered through a 0.22µ filter. Absorbance of the resulted supernatant solution was measured using U.V Visible spectrophotometer at a wavelength of 218nm against phosphate buffer pH 6.8 as blank. Concentration was calculated with the help of standard graph and total amount present in the formulation was calculated. This procedure was performed for all the formulations.

Wetting time and Water absorption ratio (R) [19-21].

Fine circular tissue papers were placed in a petri plate with a 10 cm diameter. Ten milliliters of water containing eosin, a water-soluble dye, was added to the petri plate. The dye solution is used to identify the complete wetting of the tablet surface. A tablet was carefully placed on the surface of the tissue paper in the petri plate at room temperature. The time required for water to reach the upper surface of the tablets and completely wet them was noted as the wetting time. To check for reproducibility, the measurements were carried out in replicates (n=6). The wetting time was recorded using a stopwatch.

The weight of the tablet before keeping in the petri plate was noted (W_a) using Shimadzu digital balance. The wetted tablet from the petri plate was taken and reweighed (W_b) using the same. The Water absorption ratio, R, was determined according to the following equation:

$R = 100 (W_b - W_a) / W_b$

Where $W_a$and$W_b$are the weight before and after water absorption respectively.

***In vitro* disintegration studies film/tablet** [19-21].

Disintegration time gives an indication about the disintegration characteristics and dissolution characteristics of the film/tablet. The film/tablet was placed in a petridish containing 10 ml phosphate buffer pH 6.8. The time required for the film to disintegrate completely was noted as *in vitro* disintegration time [19-21].

***In vitro* dissolution studies film/tablet** [19-21].

Dissolution test was carried out using USP rotating paddle method (apparatus II). The stirring rate was 50 rpm. Phosphate buffer pH 6.8 was used as dissolution medium (900 ml) for both films and tablets, after maintaining at 37 ± 1^0C. Samples of 5ml was withdrawn at predetermined intervals 2, 4, 6, 8, 10, 15, 20, 25 and 30 min [19-21], filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution medium, where ever necessary and were analyzed for the Lisinoprilat 218 nm by using UV spectrophotometer [22]. Each dissolution study was performed for three times and mean values were taken [23].

Results and Discussion

The overall objective of this study was to design oral disintegrating lisinporil films and tablets that disintegrate or disperse in the saliva within a few seconds.

Films

The oral disintegrating films were prepared by solvent casting technique using HPMC E15,

HPMC 50cps and HPMC 5cps (Table 1). The strips were evaluated for drug content, film thickness, average weight, *in vitro* disintegration time, *in vitro* drug release. Results are shown in table. (Table 2).

Assay was performed and the percent drug content of the batches A_3, B_1, C_1 was found to be 98±0.81%, 97.5±0.5% and 98.25±0.95% respectively, which was within the acceptable limit. All the batches were evaluated for thickness using screw guage. As different formulations contained different amount of polymers, the thickness varied in different formulations. It was found that the thickness gradually increased with the increasing amount of polymer. The thickness was found to be in the range of 0.58 – 0.66 mm

***In vitro* disintegration time of films**

Disintegration time is considered to be an important criterion in selecting the best ODF formulation. According to USP, the ODF with a disintegration time of not more than 60sec is said to be the best one [24].

Disintegration test was performed for all the batches and the disintegration time was recorded as less than 26 sec for all batches. The disintegration time of formulation A3 containing HPMC E15 was found to be lower (22.39 sec) and was selected as the best ODF formulation among other formulations.

***In vitro* dissolution studies of films:**

In vitro dissolution studies of the prepared ODFs were performed in phosphate buffer pH 6.8 using USP dissolution apparatus type-II. Results showed that all the batches released more than 90% of drug within 8min. Formulations A3, B1 and C1 have shown a drug release of 99.59±0.32%, 97.65±0.30% and 98.77±0.265 respectively, at the end of 15min. The formulation A3 was found to the be best formulation among all the others as it was found to have a disintegration time of 22.39sec and released upto 99.59±0.32% of drug after 15min. (Fig. 1)

Tablets

The tablets were prepared using various super-disintegrants like Crosspovidone, Croscarmellose sodium, Sodium starch glycollate along with other additives by direct compression method. A total number of 20 formulations were prepared and evaluated.

To achieve the best formulation, most of the excipients selected must be water soluble by nature. Selection criteria of excipients for the present study was as follows, Pearlitol SD 200 is a directly compressible grade of mannitol with good flow properties and gives a refreshing or cooling effect in the mouth due to its negative heat of solution. This excipient was used a bulking agent to achieve the desired tablet weight. Avicel 102 was included in the formulation mainly as a disintegrant at the concentrations used and to some extent as diluent. This grade of microcrystalline cellulose is granular in nature and thus displays excellent flow. To impart pleasant taste and mouth feel sodium saccharin and orange flavour were included as sweetening and flavoring agents respectively. Sodium stearyl fumerate was employed as a lubricant instead of magnesium stearate to overcome the metallic taste of the latter and also due to its water soluble nature.

Crosspovidone polymers are densely crosslinked homopolymers of N – vinyl 2 – pyrrolidones. Their porous particle morphology helps to rapidly wick liquids into the tablet by capillary action to generate the rapid volume expansion and hydrostatic pressures that cause tablet disintegration. In addition to its unique particle size and morphology, crosspovidone is non ionic and its disintegration performance will neither be influenced by pH changes in the gastrointestinal tract nor will they complex with ionic drug actives. They can also be used as solubility enhancers resulting in a faster dissolution rate without forming gels.

Croscarmellose sodium is crosslinked carboxymethyl cellulose sodium which can be used at concentrations of upto 5% as a disintegrant. Its unique fibrous nature gives excellent water wicking capabilities and crosslinking makes it hydrophilic and highly absorbent material, resulting in its swelling

properties. It rapidly swells upto 4 – 8 times its original volume on contact with water. Like crosspovidone, it is also used as a dissolution aid, hence the name Ac-Di-Sol (accelerates dissolution).

Sodium starch glycollate is a sodium salt of carboxymethyl ether of starch, usually employed at concentrations between 2 – 8% although an optimum concentration of 4% may sufficient in many cases. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling, which is its primary mechanism of action. This swells about 300 times its original volume when placed in water.

In all formulations, tablet weight and thickness were within mean ±7.5% and mean ±5% respectively. The weight variation in all the twenty formulations was found to be 78.5mg to 80.4mg, which was within pharmacopoeial limits. The thickness varies between 3.84 to 3.92 mm. Friability values were less than 1% in all cases. Hardness of all the tablets was maintained at 2.9 to 3.19 kg for all the formulations as mentioned before. Assay was performed and percent drug content of all the tablets were found to be between 97.75% and 99.36% of lisinopril, which was within the acceptable limits.

Wetting time was determined for all the formulations. The values lie between 11.16±0.75 to 57.33±0.81. The variability in wetting time for different formulations may be due to the changes in the compaction which cannot be controlled during tablet preparation and the type of the disintegrant used can also affect the wetting of the tablets. On comparing the superdisintegrants the formulations containing a combination of crosspovidone + croscarmellose sodium and crosspovidone + sodium starch glycollate took less wetting time than the other formulations containing single superdisintegrants.

Water absorption ratio ranged from 56.59% – 67.54%. Crosspovidone and croscarmellose sodium perform their disintegrating action by wicking through capillary action and fibrous structure, respectively with minimum gelling. The relative ability of the various disintegrants to wick water into the tablets was studied. After contact with water the tablets containing sodium starch glycollate swelled, and the outer edge appeared gel like. Tablets containing crosspovidone quickly wicked water and were hydrated, but were soft as compared with tablets prepared with croscarmellose sodium and sodium starch glycollate. The center of the tablets with sodium starch glycollate and croscarmellose sodium remained dry and hard.

Disintegration time is considered to be the important criteria in selecting the best ODT formulation. The *in vitro* disintegration time for all the twenty formulations varied from 17.66±0.51 to 171.83±1.16 seconds. The rapid disintegration was seen in the formulations containing crosspovidone and a combination of superdisintegrants (CP + CCS, CP + SSG). This is due to rapid uptake of the water from the medium, swelling and burst effect. It was also noticed that as the disintegrant concentration was increased from 9 to 12%, the time taken for disintegration was reduced. The disintegration time of formulation (F15) containing 5% CP + 5% CCS was found to be lower (17.66±0.51) and was selected as the best ODT formulation among all the 20 formulations.

In vitro dispersion time is a special parameter in which the time taken by the tablet for complete dispersion is measured. The time for all the twenty formulations varied between 30.66±0.81 and 259.83±1.47 sec.

The development of dissolution method for ODTs is almost similar to the approach taken for conventional tablets that utilize the taste masking. The taste masking aspect greatly influences dissolution method development, specifications, and testing. Several factors like varied thickness and pH dependent solubility of drug particle coating influence the dissolution profiles of ODTs containing taste masked actives. Since lisinopril is not bitter in taste, the metallic taste of drug was masked by using sweeteners and flavors. It has been reported that USP type II apparatus with a paddle speed of 50 rpm is commonly used for ODT formulations. Slower paddle speeds are utilized to obtain good

profiles as these formulations disintegrate rapidly.

Invitro dissolution studies of the prepared ODTs were performed in pH 6.8 phosphate buffer using USP dissolution apparatus type II. The dissolution rate was found to increase linearly with increasing concentration of super-disintegrant.

Formulations F1, F2, F3 and F4 which contained increasing concentrations of crosspovidone resulted a drug release upto 95.78%, 96.85%, 97.96 and 98.99% respectively within 20 to 30 min. Formulations F5, F6, F7 and F8 which contained increasing concentrations of croscarmellose sodium released upto 89.53%, 92.36%, 94.46% and 95.43% respectively, at the end of 30 min.

Formulations F9, F10, F11 and F12 which contained increasing concentrations of sodium starch glycollate have recorded drug release 85.4%, 88.45%, 90.4% and 92.38% respectively, at the end of 30 min.

Formulations F13, F14, 15 and F16 which contained increasing concentrations of combination of CP + CCS have recorded drug release 94.5%, 96.52%, 99.87% and 96.38% respectively, at the end of 25 to 30 min. Formulations F17, F18, F19 and F20 which contained increasing concentrations of combination of CP + SSG have recorded drug release 88.56%, 92.5%, 95.48% and 94.51 respectively, at the end of 30 min.

FTIR studies: This study revealed that there was no interaction between drug and excipients (Fig 13-22).The Fourier transform infrared spectroscopy studies were carried out for pure drug along with excipients. The results are summarized in table 13. The peaks are considered as characteristic peaks of Lisinopril. These peaks were not affected and prominently observed in IR spectra of drug and excipients. This indicates there is no interaction between drug and excipients.

Table 1. Formulations of films

Ingredients	A1 HPMC E15 (1:1.5)	A2 HPMC E15 (1:1.75)	A3 HPMC E15 (1:2)	B1 HPMC 5cps (1:2)	C1 HPMC 50cps (1:2)
Lisinopril (mg)	88.55	88.55	88.55	88.55	88.55
Polymer (mg)	132.82	154.95	177	177	177
Poly Ethylene Glycol – 400 (ml)	0.1	0.1	0.2	0.2	0.2
Orange flavor (mg)	10	10	10	10	10
Sodium saccharin (mg)	10	10	10	10	10
Water (ml)	15	15	15	15	15

All batches were casted on Petri plate to provide 8 strips with dimension 3.79 cm^2 after drying.

Table 2. Physical evaluation of films

Formulation Code	**Mean weight (mg)**	**Mean thickness (mm)**	**Disintegration time (sec)**	**Assay (%)**
A3	16±0.81	0.6±0.008	22.39±0.23	98±0.81
B1	15±0.81	0.59±0.012	24.38±0.26	97.5±0.577
C1	15.5±0.57	0.58±0.005	25.40±0.24	98.25±0.95

Table 3: Formulation codes of ODT

Disintegrant used	**Concentration (%)**	**Formulation code**
Crosspovidone	3	F1
	6	F2
	9	F3
	12	F4
Croscarmellose sodium	3	F5
	6	F6
	9	F7
	12	F8
Sodium starch glycolate	3	F9
	6	F10
	9	F11
	12	F12

Crosspovidone + crosscarmellose sodium	6 (3:3) 8 (4:4) 10 (5:5) 12 (6:6)	F13 F14 F15 F16
Crosspovidone + sodium starch glycolate	6 (3:3) 8 (4:4) 10 (5:5) 12 (6:6)	F17 F18 F19 F20

Table 4. Formulae of lisinopril ODTs prepared by direct compression method with various superdisintegrants

Ingredients	**Super disintegrants concentration (%) of Crosspovidone/ Croscarmellose Sodium/ Sodium Starch Glycollate**			
	3%	6%	9%	12%
Lisinopril	5	5	5	5
Super disintegrants	2.4	4.8	7.2	9.6
Avicel PH 102	54.6	52.2	49.8	47.4
Pearlitol SD200	10	10	10	10
Sodium saccharin	5	5	5	5
Orange flavor	2	2	2	2
Sodium stearyl fumerate	0.5	0.5	0.5	0.5
Talc	0.5	0.5	0.5	0.5
Total weight (mg)	80	80	80	80

Table 5: Formulae of lisinopril ODTs prepared with combination of superdisintegrants

Ingredients	**CP + CCS**				**CP + SSG**			
	6%	**8%**	**10%**	**12%**	**6%**	**8%**	**10%**	**12%**
Lisinopril	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**
Superdisintegrants	**4.8**	**6.4**	**8**	**9.6**	**4.8**	**6.4**	**8**	**9.6**
Avicel PH 102	**52.2**	**50.6**	**49**	**47.4**	**52.2**	**50.6**	**49**	**47.4**
Pearlitol SD200	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Sodium saccharine	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**
Orange flavor	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**

Sodium stearyl fumerate	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**
Talc	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**
Total weight (mg)	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**

Note: CP – Crosspovidone, CCS – Croscarmellose Sodium, SSG – Sodium Starch Glycollate

Table 6: Preformulation characteristics of lisinopril ODTs

Formulation	**Bulk density (g/cc)**	**Tapped density (g/cc)**	**Hausner ratio**	**Compressibilty index (%)**	**Angle of repose (ɵ)**
F1	0.435	0.522	1.20	16.66	32.67
F2	0.429	0.518	1.20	17.18	29.08
F3	0.430	0.524	1.21	17.93	31.78
F4	0.432	0.528	1.22	18.18	30.64
F5	0.428	0.518	1.21	17.37	30.36
F6	0.420	0.510	1.21	17.64	31.05
F7	0.416	0.509	1.22	18.27	32.54
F8	0.417	0.515	1.23	19.02	29.67
F9	0.425	0.515	1.21	17.47	31.85
F10	0.421	0.509	1.20	17.28	29.56
F11	0.419	0.515	1.22	18.64	30.17
F12	0.415	0.512	1.23	18.94	32.08

Table 7: Pre formulation characteristics of lisinopril ODTs prepared with combination of superdisintegrants

Formulation	**Bulk density (g/cc)**	**Tapped density (g/cc)**	**Hausner ratio**	**Compressibilty index (%)**	**Angle of repose (ɵ)**
F13	0.420	0.520	1.23	19.23	29.67
F14	0.423	0.512	1.21	17.38	29.54
F15	0.435	0.520	1.20	16.34	31.76
F16	0.422	0.512	1.21	17.57	32.04
F17	0.425	0.523	1.23	18.73	30.56
F18	0.434	0.526	1.21	17.49	31.23
F19	0.426	0.512	1.20	16.79	29.52
F20	0.420	0.519	1.23	19.07	29.32

Table 8: Tabletting characteristics of lisinopril ODTs

Formulation	Weight (mg)	Drug content (%)	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)
F1	79.9±0.70	98.96±0.47	3.05±0.13	0.48	3.84±0.032
F2	79.52±0.85	99±0.65	3.10±0.15	0.53	3.85±0.028
F3	78.9±0.52	99.11±0.52	2.95±0.08	0.44	3.86±0.024
F4	80.2±1.17	99.15±0.60	2.95±0.10	0.57	3.86±0.051
F5	79.0±0.49	99.2±0.4	3.08±0.12	0.43	3.88±0.048
F6	78.8±0.58	98.85±0.58	3.11±0.14	0.56	3.90±0.052
F7	79.3±0.54	99.31±0.24	2.92±0.08	0.53	3.92±0.038
F8	80.4±1.0	98.96±0.28	3.0±0.09	0.45	3.91±0.042
F9	79.6±0.95	99.3±0.38	2.9±0.07	0.6	3.90±0.040
F10	79.2±0.97	99.36±0.29	3.05±0.08	0.49	3.89±0.042
F11	79.4±0.86	98.75±0.40	3.05±0.09	0.53	3.89±0.034
F12	78.5±0.42	99.21±0.38	2.93±0.08	0.58	3.87±0.031

Table 9: Tabletting characteristics of lisinopril ODTs prepared with combination of superdisintegrants

Formulation	Weight (mg)	Drug content (%)	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)
F13	80.3±1.18	98.56±0.49	3.19±0.05	0.47	3.86±0.034
F14	79.3±0.53	98.61±0.60	3.16±0.04	0.52	3.86±0.023
F15	80.1±0.75	98.98±0.56	3.10±0.10	0.63	3.87±0.044
F16	80.3±0.86	99.03±0.58	3.05±0.09	0.58	3.89±0.051
F17	79.1±0.84	97.75±0.69	3.15±0.04	0.58	3.85±0.029
F18	78.8±0.56	98.76±0.56	2.92±0.08	0.53	3.88±0.046
F19	79.6±0.60	99.08±0.29	3.00±0.09	0.51	3.86±0.025
F20	80.0±0.75	98.86±0.39	3.12±0.12	0.55	3.84±0.034

Table 10: Tabletting characteristics of lisinopril ODTs

Formulation	Wetting time (sec)	*In vitro* dispersion time (sec)	Disintegration time (sec)	Water absorption ratio (%)
F1	24.83±0.98	221.33±1.03	116.5±1.37	58.45
F2	21.16±0.75	180.5±1.04	95.16±0.75	59.25
F3	14.66±0.51	75±0.89	56.50±1.64	58.9

F4	**11.66±0.51**	**54±0.63**	**27.83±1.16**	**60.65**
F5	57.33±0.81	244.5±1.04	168.83±1.94	59.88
F6	22.33±1.36	215.5±0.54	98±0.63	61.48
F7	28±1.09	177.83±1.16	73.16±1.47	59.55
F8	19.66±0.81	126.66±0.81	36.66±1.21	60.01
F9	37.33±0.81	259.83±1.47	171.83±1.16	64.37
F10	28.33±0.81	225.33±0.81	153±0.89	67.54
F11	26.66±0.81	186.83±0.75	81.5±1.04	65.50
F12	36.83±1.16	154.5±0.83	42.66±1.75	65.89

Table 11: Tabletting characteristics of lisinopril ODTs prepared with combination of superdisintegrants.

Formulation	**Wetting time (sec)**	***In vitro* dispersion time (sec)**	**Disintegration time (sec)**	**Water absorption ratio (%)**
F13	19.33±0.51	91.66±1.21	82.5±1.04	59.49
F14	14.33±0.51	49.33±1.03	46±0.89	56.59
F15	**11.16±0.75**	**30.66±0.81**	**17.66±0.51**	**57.08**
F16	12.5±0.54	35.16±0.75	20.33±0.81	58.72
F17	19.1±0.75	96.83±0.40	86.16±0.75	57.95
F18	14.83±0.75	54.16±1.72	47.5±1.04	60
F19	11.5±0.54	46.66±0.81	23.66±0.51	61.50
F20	13±0.89	43.83±0.75	20.83±1.16	58.24

Table 12: Cumulative percent lisinopril released from ODTs containing varying concentrations of different superdisintegrants.

Cumulative percent (±S.D.) drug released						
Time (min)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
2	27.35±0.28	22.35±0.52	20.46±0.25	28.31±0.23	18.35±0.34	15.43±0.30
4	40.33±0.28	34.36±0.28	29.28±0.19	41.33±0.24	25.5±0.28	23.43±0.32
6	55.46±0.31	45.31±0.27	42.35±0.25	59.33±0.26	37.36±0.25	37.36±0.26
8	69.46±0.27	62.35±0.25	61.31±0.23	73.48±0.34	57.41±0.23	54.38±0.26
10	74.38±0.27	75.48±0.30	76.4±0.36	85.38±0.34	64.55±0.28	67.38±0.37
15	83.35±0.20	87.4±0.31	82.53±0.30	98.6±0.29	72.48±0.35	75.46±0.26
20	94.45±0.30	96.31±0.29	97.31±0.20	98.89±0.32	80.45±0.28	82.31±0.23

25	94.89±0.24	96.57±0.28	97.76±0.28	98.95±0.24	86.5±0.26	87.48±0.24
30	95.78±0.27	96.85±0.32	97.96±0.25	98.99±0.23	89.53±0.19	92.36±0.25

Cumulative percent (±S.D.) drug released						
Time (min)	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
2	22.33±0.25	14.38±0.31	19.33±0.20	23.43±0.16	18.48±0.33	19.4±0.32
4	33.36±0.31	22.1±0.59	28.36±0.32	35.31±0.27	27.18±0.18	27.41±0.26
6	45.46±0.26	36.43±0.30	36.45±0.25	47.36±0.29	34.43±0.23	35.28±0.29
8	62.43±0.23	55.46±0.30	49.43±0.26	53.5±0.34	45.61±0.17	52.43±0.26
10	70.28±0.20	62.46±0.25	55.48±0.26	64.45±0.30	52.41±0.36	65.41±0.33
15	78.41±0.26	75.58±0.27	68.46±0.32	72.6±0.27	61.25±0.55	78.45±0.35
20	86.28±0.24	80.4±0.26	74.58±0.27	78.41±0.14	70.46±0.21	84.51±0.24
25	90.28±0.17	83.48±0.30	78.43±0.27	83.45±0.28	75.41±0.24	88.36±0.18
30	94.46±0.25	95.43±0.19	85.4±0.22	88.45±0.18	90.4±0.33	92.38±0.19

Table 13: Table showing the wavelength regions of each ingredient in IR spectra.

IR Spectra	Peak of Functional groups [Wave length (cm^{-1})]				
	C-H Stretching (alkane)	C-H Bending (aromatic)	C=O Stretching (Phenols)	C=O Stretching (Amide)	C=C Stretching (Aromatic)
Lisinopril	2925.3	749.27	1395	1656.38	1590
Lisinopril + CCS	2850	760	1400	1654.67	1590
Lisinopril + CP	2900	750	1390	1650	1580
Lisinopril + SSG	2840	760	1400	1650	1580
Lisinopril + HPMC E15	2900	750	1400	1659.12	1590
Lisinopril + HPMC 5 Cps	2900	760	1390	1650	1580
Lisinopril + HPMC 50 Cps	2900	750	1390	1654.75	1580

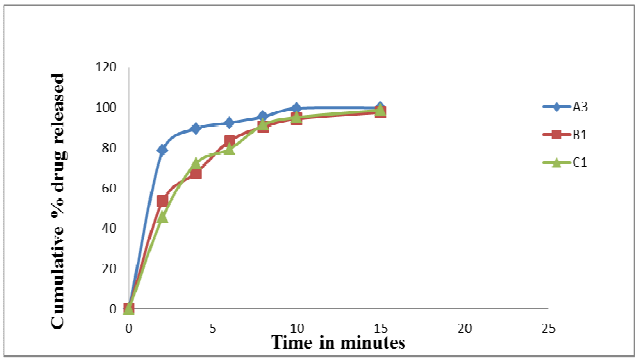

Figure 1: Graphical representation of Cumulative Percent Release of Lisinopril - ODF formulation.

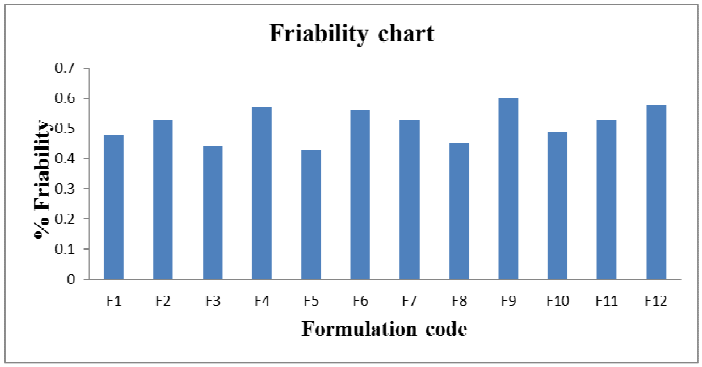

Figure 3a: Graphical representation of friability of lisinopril ODTs prepared by varying concentrations of superdisintegrants.

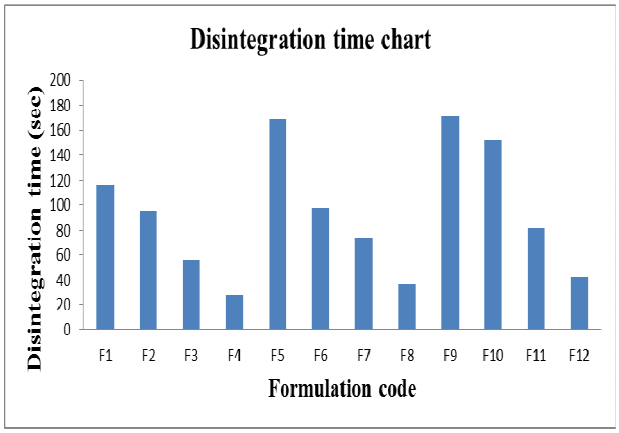

Figure 2a: Graphical representation of disintegration times of lisinopril ODTs prepared by varying concentrations of superdisintegrants.

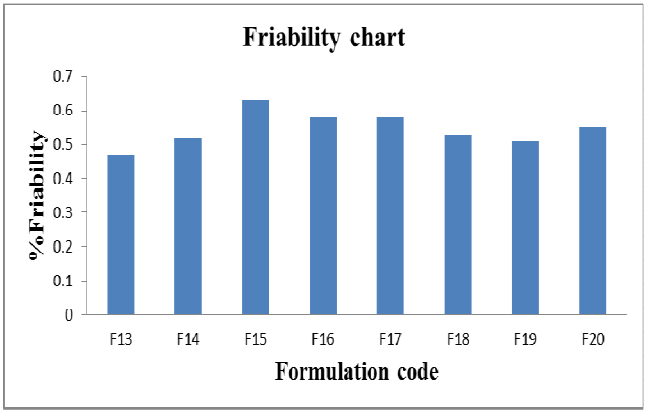

Figure 3b: Graphical representation of friability of lisinopril ODTs prepared by varying concentrations of superdisintegrants.

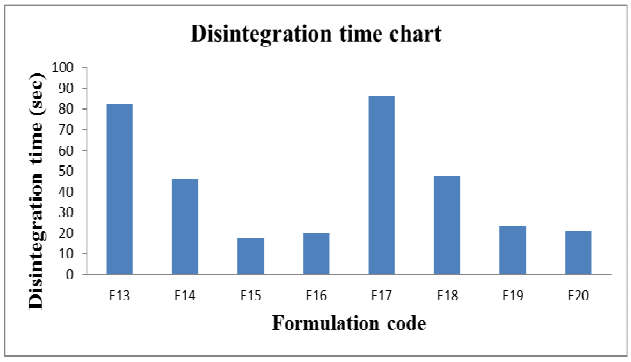

Figure 2b: Graphical representation of disintegration times of lisinopril ODTs prepared by varying concentrations of superdisintegrants.

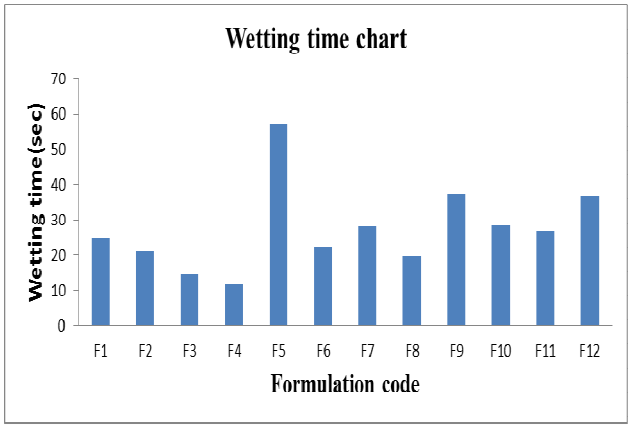

Figure 4a: Graphical representation of wetting time of lisinopril ODTs prepared by varying concentrations of superdisintegrants.

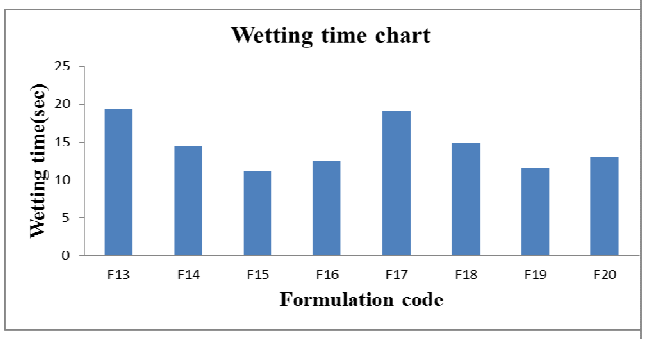

Figure 4b: Graphical representation of wetting time of lisinopril ODTs prepared by varying concentrations of superdisintegrants.

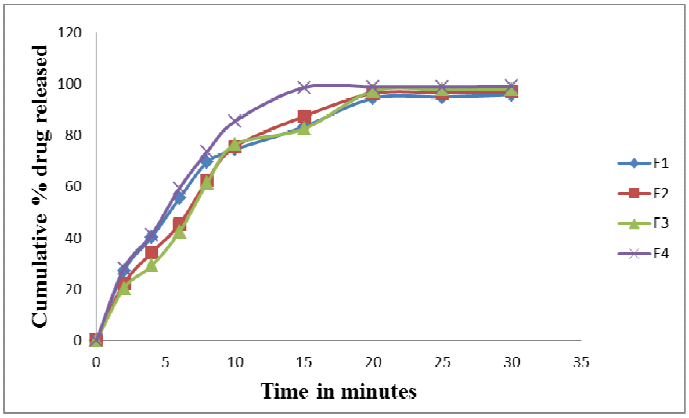

Figure 5: Graphical representation of Cumulative percent lisinopril released from ODTs containing varying concentrations of crosspovidone.

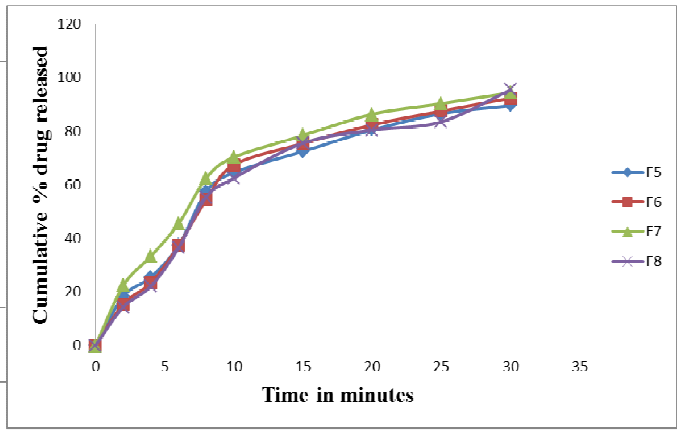

Figure 6: Graphical representation of Cumulative percent lisinopril released from ODTs containing varying concentrations of croscarmellose sodium.

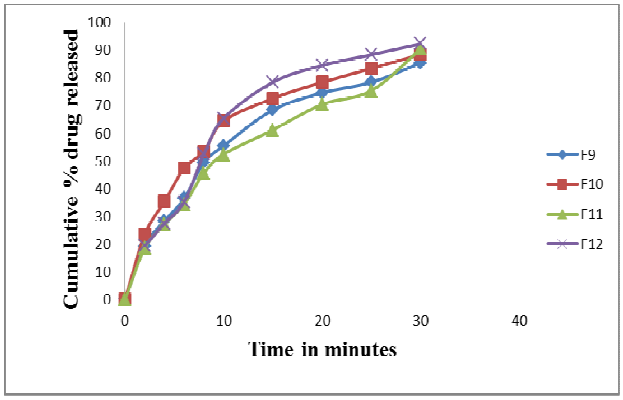

Figure 7: Graphical representation of Cumulative percent lisinopril released from ODTs containing varying concentrations of sodium starch glycollate.

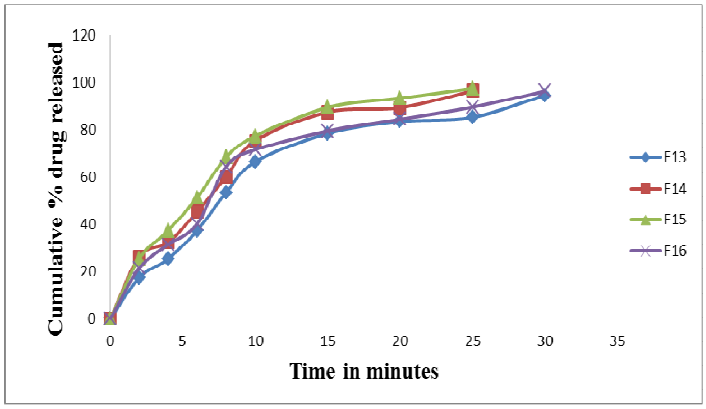

Figure 8: Graphical representation of Cumulative percent lisinopril released from ODTs containing varying concentrations of CP + CCS.

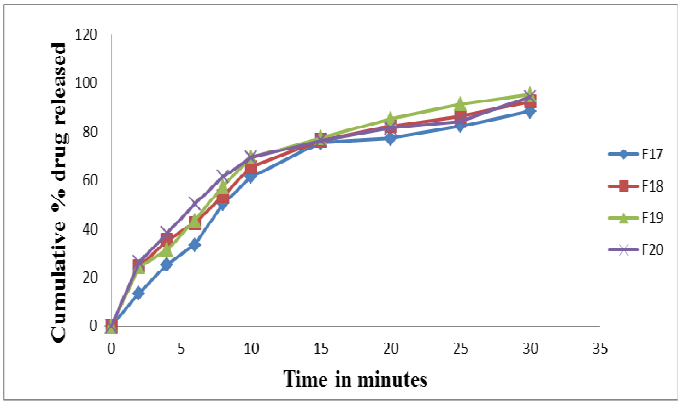

Figure 9: Graphical representation of Cumulative percent lisinopril released from ODTs containing varying concentrations of CP + SSG.

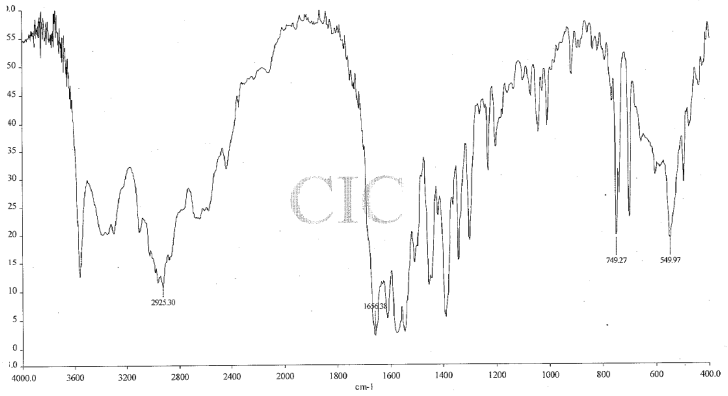

Figure 10: FTIR spectra of lisinopril.

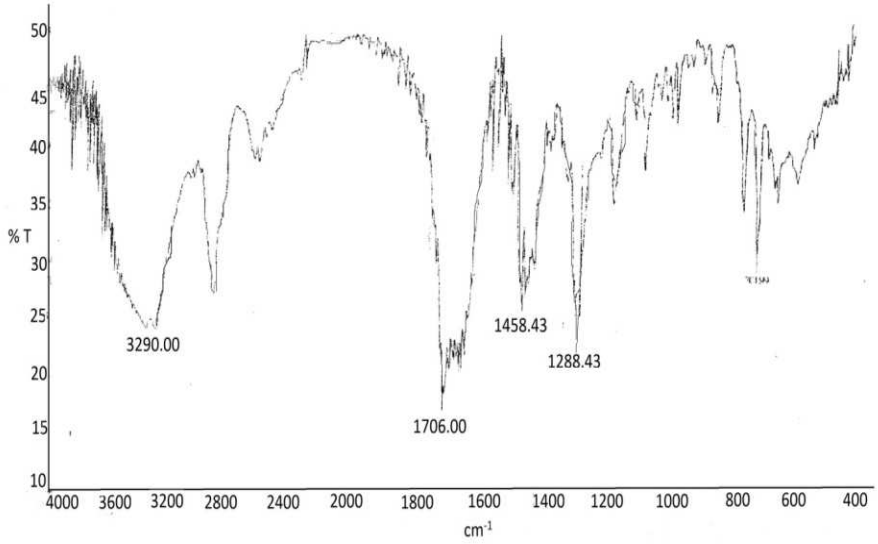

Figure 11: FTIR spectra of crosspovidone

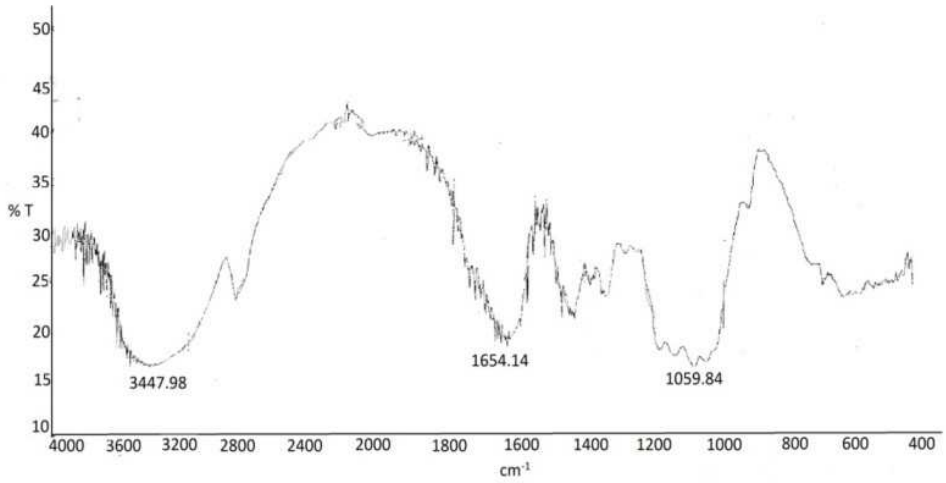

Figure 12: FTIR spectra of croscarmellose sodium

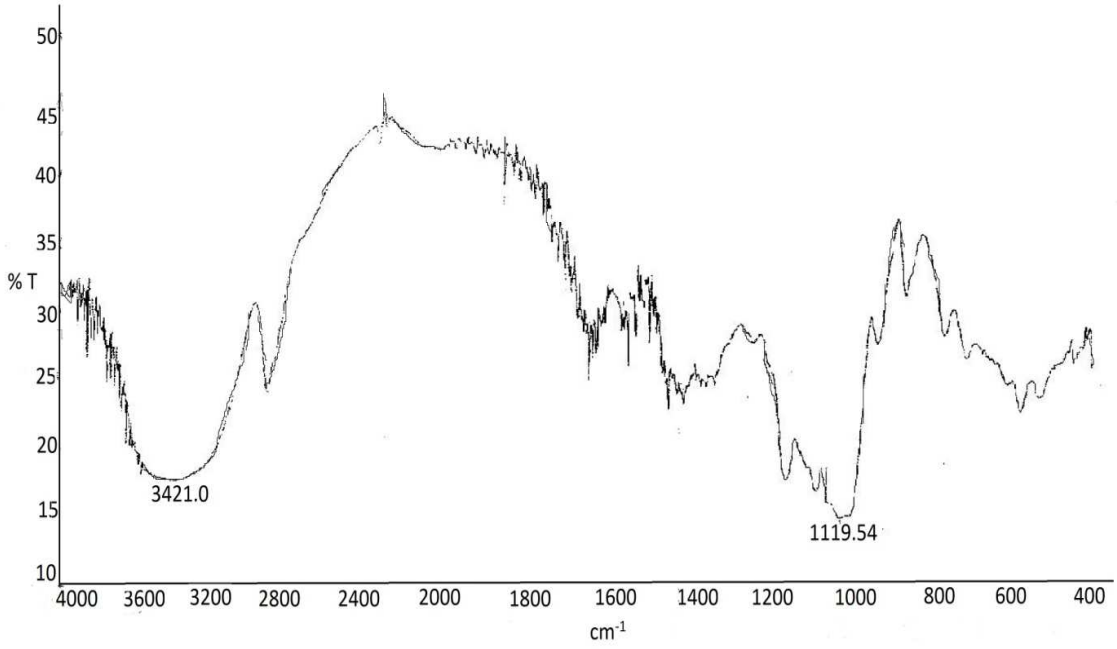

Figure13: FTIR spectra of sodium starch glycolate

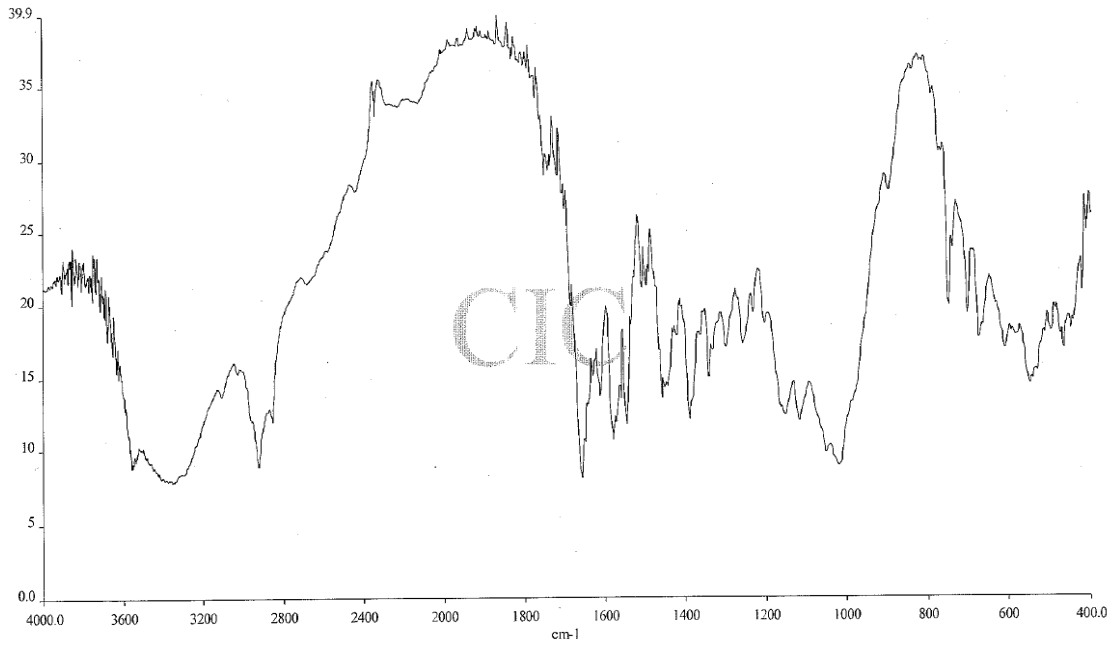

Figure 14: FTIR spectra of physical mixture of lisinopril and crospovidone

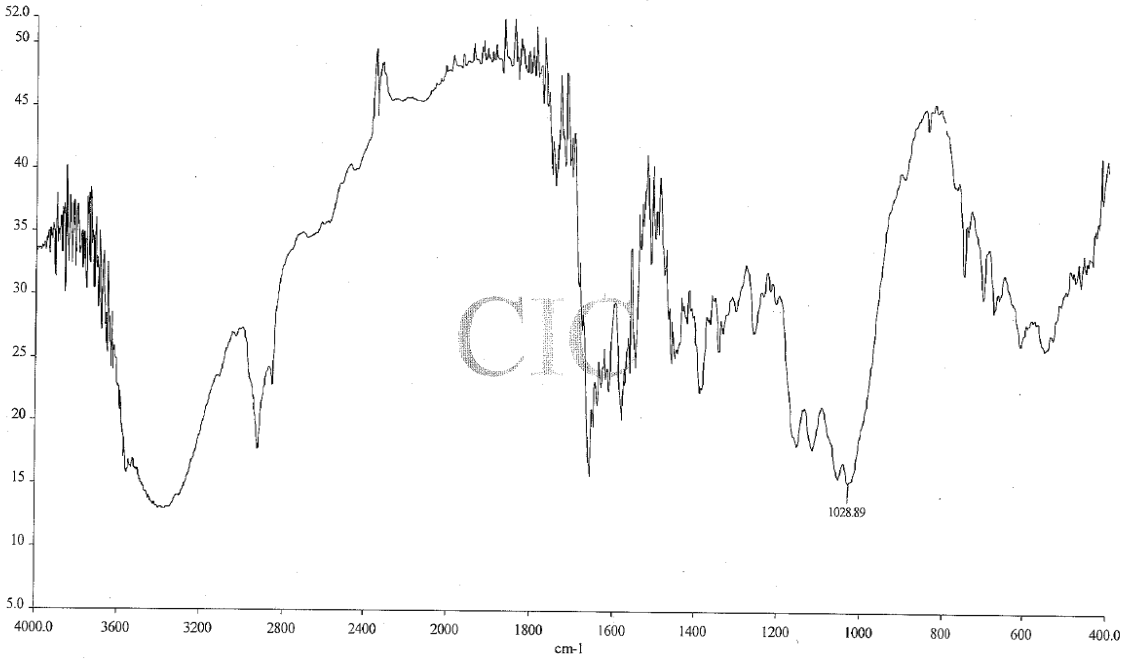

Figure 15: FTIR spectra of physical mixture of lisinopril and sodium starch glycolate

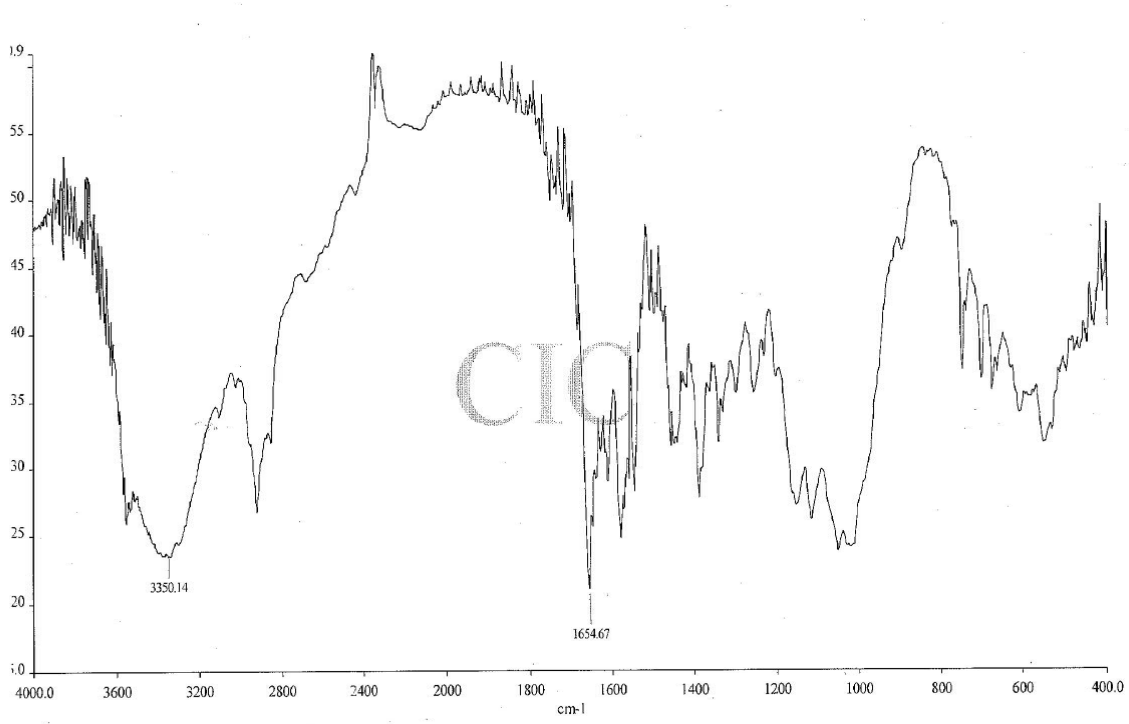

Figure 16: FTIR spectra of physical mixture of lisinopril and croscarmellose sodium

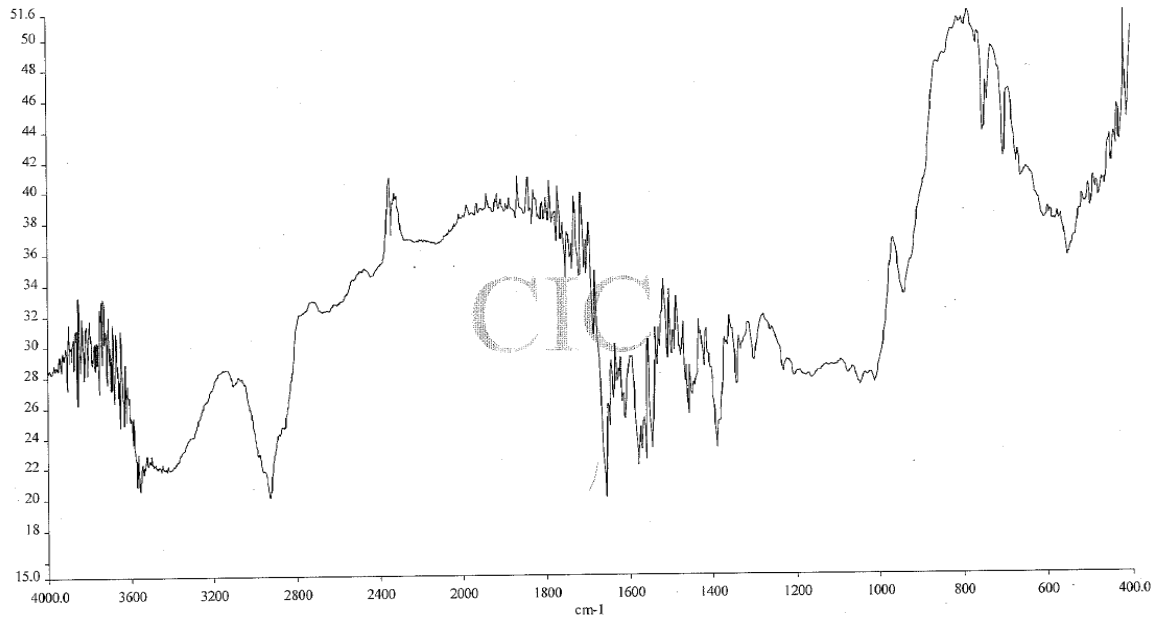

Figure 17: FTIR spectra of HPMC 5CPs and Lisinopril

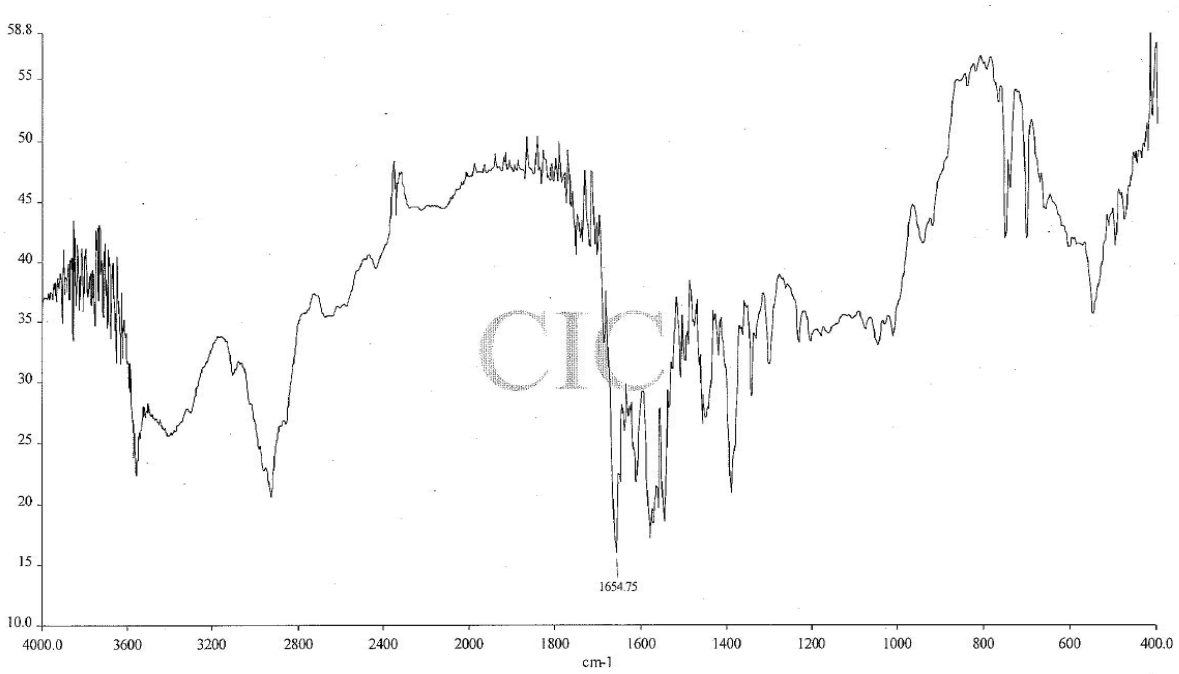

Figure 18: FTIR spectra of HPMC 50CPs and Lisinopril

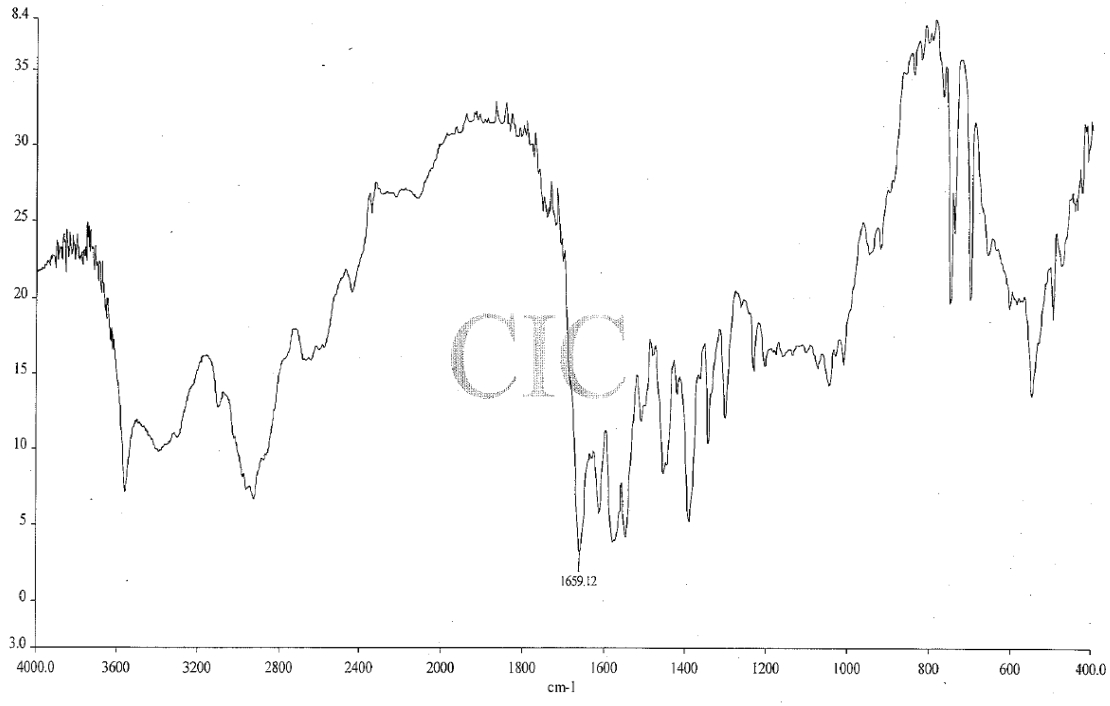

Figure 19: FTIR spectra of HPMC E – 15 and Lisinopril

Conclusion

Lisinopril Oral Disintegrating Tablets were prepared by direct compression method using crosspovidone, croscarmellose sodium, sodium starch glycollate and combinations of CP + CCS, CCS + SSG and CP + SSG as superdisintegrants. The formulation F15 was found to be the best with faster disintegration time (17.66 sec) and 99.87±0.18% drug release at the end of 25min. Of the three ODF formulations, formulation A3 exhibited faster disintegration time (22.39 sec) than formulations B1 and C1. Moreover formulation A3 showed 99.59±0.32% drug release at the end of 15 min. So ODF formulated with HPMC E15 (A3) was the best formulation. Based on disintegration and dissolution results it was concluded that the formulation F15 containing CP 5% + CCS 5% was the best formulation among the ODT and A3 containing HPMC E15 was the best among ODF formulations. On comparing the ODT and ODF, lisinopril ODT was drug release found to have a faster disintegration time and a better drug release than ODF.

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