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Formulation and evaluation of mouth dissolving tablets containing losartan potassium

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ABSTRACT

The objective of the proposed research work is to prepare and evaluate the mouth dissolving/disintegrating tablets (MDTs) of losartan Potassium, which avoid the first-pass metabolism, improved the dissolution rate and enhance the bioavailability. Losartan potassium is an angiotention receptor antagonist, used in the management of hypertension. Mouth dissolving tablets (MDTs) were prepared by direct compression method by using different concentrations of superdisintegrant like Crospovidone, Sodium Starch Glycolate , Croscarmellose sodium, Micro Crystalline Cellulose and evaluated for physicochemical evaluation parameter such as hardness, friability, weight variation, drug content uniformity, water absorption ratio, wetting time, in-vitro, in-vitro dissolution studies. The twelve formulations, F1-F9 were formulated and among these formulations, F3 was optimized. The hardness, friability, weight variation and drug content were found to be within pharmacopeias limits. The In vitro drug release from formulation containing super disintegrant CP was found between 87.64±0.36 to 98.75±0.61 in 10 min and the maximum drug release was found with F3 formulation. The disintegration studies shown that the all formulations disintegrated in less than 1 minute. The formulation F3 shown less disintegration time of 17 seconds. The croscarmellose sodium and sodium starch glycolate shown more disintegration time than crospovidone. An accelerated stability study on optimized formulation was performed. The formulation was found to be stable, there was no change in the hardness, friability, disintegration time, and In-vitro drug release pattern. DSC and FTIR data revealed that no interactions takes place between the drug and polymers used in the optimized formulation. In conclusion, it can be stated that the objective of the study has been achieved. From the above study the formula used for F3 formulation was concluded as an optimized formulation due to its less disintegration time and good % drug release when compared with other formulations.

Keywords: losartan Potassium, Mouth dissolving tablets (MDTs), Crospovidone, Sodium Starch Glycolate

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INTRODUCTION

Tablet is the most popular among dosage forms existing today because of its convenience of self-administration, compactness and easy manufacturing. In the recent past several novel technologies have emerged with improved performance, improved patient compliance and reduced adverse effects. One such approach is to formulate mouth-dissolving tablets or mouth-disintegrating tablets which are dissolves rapidly in saliva without the need of water within few seconds due to the action of superdisintegrant in the formulations. The demand for mouth dissolving tablets has been growing over the other oral dosage forms (such as tablets, capsule, dry syrups, chewing gums/chewable tablets) among pediatric, geriatric, dysphasic, psychotic and non-cooperative patients and travelers. The basic approach used in development of mouth dissolving tablets is the use of superdisintegrant, which provide instantaneous disintegration of tablets after putting on tongue, thereby releasing the drug in saliva. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form [1]. To design rapidly disintegrating oral tablets of Losartan potassium for pediatric patients and elderly patients, in order to improve bioavailability, ease of administration and patient compliance. Losartan potassium indicated for

hypertension, diabetic nephropathy and heart attacks disorders [2, 3]. The bioavailability of Losartan is 33% due to extensively first pass metabolism [4, 5, 6]. The terminal t1/2 of losartan is 2h. Various techniques can be used to formulate rapidly disintegrating or dissolving tablets [7,8] The objective of the proposed research work is to prepare and evaluate the mouth dissolving/disintegrating tablets (MDT) of losartan Potassium, which avoid the first-pass metabolism and enhance the bioavailability.

MATERIALS AND METHODS

Losartan potassium was obtained as gift sample from Dr. Reddy's Laboratories, Hyderabad, Ac-Di-sol& Primogel was obtained from Colorcon Asia Pvt. Ltd. Goa, Polyplasdone-xl was obtained from Merck chemicals Ltd.,Mumbai, Sodium saccharine, Mannitol, Micro crystalline cellulose, Talc and Magnesium stearate were obtained from S.D. Fine Chemicals. Pvt Ltd, Mumbai, India. All chemicals and solvents used were of analytical grade.

Experimental methodology:
Losartan potassium drug was selected, which is required to show immediate therapeutic action. The basic approach used to study and evaluation of Mouth dissolving tablet. For this study different superdisintegrants like crospovidone, croscarmellose and sodium starch glycolate were selected to formulate the Mouth dissolving tablets of Losartan potassium by direct compression technique.

Preparation of standard curve for Losartan potassium in 6.8 pH buffer
Accurately weighed amount (100 mg) of the drug was dissolved in 6.8 pH buffer in 100 ml volumetric flask and the volume was made up to 100 ml. from this stock solution10ml is withdrawn in to volumetric flask, made the volume up to 100ml with distilled water. From this 2nd stock solution (100mcg/ml) withdrawn 0.2, 0.4, 0.6, 0.8, 1ml and made up to 10ml with 6.8pH buffer. It gives concentrations of 2, 4, 6, 8, 10µg/ml solutions and the corresponding absorbance was measured at 254nm in a UV/Visible spectrophotometer.

Pre formulation Studies
Pre formulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms.

Pre compression parameters of the powder blend
Preparation of mixed blend of drug and excipients:
All the ingredients were passed through mesh no 60. Required quantity of each ingredient was taken for each specified formulation and all the ingredients were subjected to grinding to a required degree of fineness. The powder blend was subjected to pre compression parameters.

Angle of repose:
This is the maximum angle possible between the surface pile of powder and horizontal plane. The frictional forces in the lose powder can be measured by angle of repose. The tangent of angle of repose is equal to the co-efficient friction (µ) between the particles. Hence the rougher & more irregular the surface of particles the greater will be angle of repose.

Procedure: Weigh accurately 100g of the blend and are carefully poured through the funnel whose tip is secured at a height of 2.5cm above the graph paper which is placed on a horizontal surface. The granules are poured until the apex of the conical pile just touches the tip of the funnel.

Angle of repose is calculated by the following formula.

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

Where, θ = angle of repose, r=radius of the pile, h=height of the pile,

Bulk density:
Apparent bulk density (*b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V*) and weight of the powder (M) was determined. The bulk density was calculated using the formula.

$$*b = M/V*$$

Tapped density:
The measuring cylinder containing a known mass of blend was tapped for a fixed time (around 250). The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (*t) was calculated using the formula

$$*t=M/V_t$$

Compressibility index:
The simplest way for measurement of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (C.I) which is calculated using the formula,

$$C.I\ (\%) = \frac{\text{Tapped density} - \text{Bulk density} \times 100}{\text{Tapped density}}$$

Hausner's ratio:
Hausner ratio is an indirect index of ease of powder flow. It is calculated by the using the formula,

$$\text{Hausner ratio} = *dt/*db$$

Where *dt=tapped density.*db=bulk density

Preparation of Losartan potassium of Mouth dissolving tablets:
All ingredients were triturated individually in a mortar and passed through #60 sieves, Then required quantity of all ingredients were weighed for a batch size of 50 tablets and mixed uniformly in a mortar except talc and magnesium stearate. Finally magnesium stearate and talc were added as lubricant. This uniformly mixed blend was compressed in to tablets containing 25mg drug using 10mm flat face surface punches on a cemache rotary tablet machine by direct compression method. Total weight of tablet was kept 250mg.

Table 1: Formulations of Losartan potassium containing different super disintegrants

Ingredients (mg)	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Losartan potassium	25	25	25	25	25	25	25	25	25
Mannitol	149	149	149	149	149	149	149	149	149
MCC	56	54	52	56	54	52	56	54	52
CP	8	10	12	---	---	---	---	---	---
CCS	---	---	---	8	10	12	---	---	---
SSG	---	---	---	---	---	---	8	10	12
Aspartame	8	8	8	8	8	8	8	8	8
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Total	250	250	250	250	250	250	250	250	250

CP= Crospovidone, SSG=Sodium Starch Glycolate , CCS = Croscarmellose sodium, Mcc = Micro Crystalline Cellulose

Evaluation of Fast disintegrating tablets
Weight variation: Twenty tablets were randomly selected and average weight was determined. Then individual tablets were weighed and percent deviation from the average was calculated.

Table 2: Percentage deviation allowed for the tablets

Pharmaceutical Form	Avg. Weight	% Deviation
Tablets	130 mg or less	10
	More than 130 mg	7.5
	More than 324 mg	5

Thickness [9]
Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by vernier callipers scale.

The thickness of the tablet related to the tablet hardness and can be used an initial control parameter. Tablet thickness should be controlled within a ± 5% variation of a standard value. In addition, thickness must be controlled to facilitate packaging. The thickness in millimetres (mm) was measured individually for 10 pre weighed tablets by using screw gauge. The average thickness and standard deviation were reported.

Hardness [9]

The strength of tablet is expressed as tensile strength (Kg/cm^2). The tablet crushing load, which is the force required to break a tablet into pieces by compression. It was measured using a tablet hardness tester. Three tablets from each formulation batch were tested randomly and the average reading noted.

Friability [9]

Friability of the tablets was determined using Roche Friabilator (Electrolab, India). This device consists of a plastic chamber that is set to revolve around 25 rpm for 4 minutes dropping the tablets at a distance of 6 inches with each revolution. Pre weighed sample of 20 tablets was placed in the Friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F %) is given by the formula

$$F\ \% = (1-W_0/W)\times 100$$

Where, W_0 is weight of the tablets before the test and W is the weight of the tablets after test

Wetting time [10]

Five circular tissue papers of 10-cm diameter were placed in a petridish with a 10-cm diameter. 10 ml of water at $37^0C \pm 0.5^0C$ containing eosin, a water-soluble dye, was added to the petridish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time. Six tablets from each formulation batch were tested randomly and the average reading noted.

Water absorption ratio [10]

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed.

Water absorption ratio R, was determined using following equation

$$R = W_a - W_b / W_b \times 100$$

Where W_a = weight of tablet after absorption
W_b = weight of tablet before absorption

Content uniformity

20 tablets were randomly selected and average weight was calculated. Tablets were powdered in a glass mortar. Powder equivalent to 25mg was weighed and dissolved in 100 ml of 6.8 pH buffer filtered and drug content analyzed spectrophotometrically at 254nm.

***In-vitro* disintegration time:**

The USP device to rest disintegration was six glass tubes that are "3 long, open at the top, and held against 10" screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1 litre beaker of buffer at $37 \pm 2\ ^0C$, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.

***In-vitro* release studies:**

In vitro drug release of Losartan potassium Mouth dissolving tablets was determined using USP Dissolution Apparatus II (Paddle type) (Electrolab TDT-08L). The dissolution test was performed using 900 ml 6.8 pH buffer at $37^0C \pm 0.5^0C$. The speed of rotation of paddle was set at 50 rpm. 5 ml samples were withdrawn at time points of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10min and same volume was replaced with fresh media. Absorbance of solution was checked by UV spectrophotometer (ELICO- 164 double beam spectrophotometer, Hyderabad, India) at a wavelength of 254 nm and drug release was determined from standard curve.

Accelerated stability studies:

The optimized formulation was subjected to stability studies at $40^0C \pm 75\%RH$ for period of three months. Each tablet was individually wrapped in aluminum foil and packed in ambered colored bottle and put at above specified condition in a heating humidity chamber for three months. For every one month tablets were analyzed for the hardness, friability disintegration time, and drug content and *in-vitro* drug release. The results are obtained within the limits.

Drug-excipients compatibility study by FTIR

The spectrum analysis of pure drug and physical mixture of drug and different excipients which are used for preparation of tablets was studied by FTIR. FTIR spectra were recorded by preparing potassium bromide (KBr)

disks using a Shimadzu Corporation (Japan) facility (model - 8400S). Potassium bromide (KBr) disks were prepared by mixing few mg of sample with potassium bromide by compacting in a hydrostatic press under vacuum at 6-8 tons pressure. The resultant disc was mounted in a suitable holder in IR spectrophotometer and the IR spectrum was recorded from 4000 cm^{-1} to 400 cm^{-1} in a scan time of 12 minutes. The resultant spectrum was compared for any spectral changes. They were observed for the presence of characteristic peaks for the respective functional group in the compound.

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. The DSC thermograms were recorded for pure drug, SSG, Crospovidone, Croscarmellose sodium and optimized formulation. Accurately weighed samples were placed on aluminium plate, sealed with aluminium lids and heated at a constant rate of 5ºC /min, over a temperature range of 0 to 250ºC.

RESULTS AND DISCUSSION

Pre compression parameters of all formulations blend were conducted for angle of repose, bulk density, tapped density, compressibility index, *Hausner's* ratio. The two most +important attributes for the direct compression formula are good flow and good compressibility. Inter particulate interactions that influence the bulking properties of a powder with powder flow. A comparison of the bulk density and tapped density can give a measure of the relative importance of this interaction in a given powder, such a comparison is often used as an index of the ability of the powder to flow. The angle of repose gives important information about the flow characteristics of the powder mixture. The powder flow depends on three general areas: the physical properties of the particle (e.g., shape, size, compressibility), the bulk powder properties (e.g., size distribution, compaction), and the processing environment (e.g., storage, humidity).

Table 3: Pre formulation studies of blend of all formulation

Formulation code	Angle of repose (θ)	Bulk density (g/cm3)	Tapped density (g/cm3)	Compressibility index (%)	Hausner's ratio
F1	22.4±0.02	0.49±0.03	0.57±0.05	16.1±0.02	1.12±0.03
F2	21.2±0.04	0.51±0.04	0.56±0.03	15.9±0.04	1.11±0.01
F3	19.7±0.06	0.51±0.05	0.57±0.04	17.6±0.01	1.19±0.04
F4	18.8±0.03	0.54±0.06	0.60±0.06	13.2±0.06	1.15±0.05
F5	17.2±0.04	0.52±0.03	0.56±0.04	14.8±0.06	1.18±0.04
F6	19.2±0.05	0.53±0.05	0.58±0.05	15.4±0.09	1.21±0.07
F7	19.8±0.6	0.51±0.06	0.55±0.02	14.4±0.08	1.16±0.04
F8	17.6±0.04	0.50±0.08	0.54±0.06	16.4±0.09	1.19±0.06
F9	17.2±006	0.49±0.07	0.50±0.03	17.9±0.07	1.21±0.08

Evaluation studies of tablets

Table 4: Evaluation of tablets

Formulation code	Weight variation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content	Disintegration (sec)	Water absorption ratio	Wetting time(sec)	Drug release (%)
F1	250.2±0.5	1.4±0.03	3.14± 0.02	0.39±0.03	98.23	24±0.31	49.42± 0.34	29.21±0.34	94.19±0.41
F2	249.4±0.6	1.3±0.02	3.16±0.12	0.37± 0.07	97.89	20 ±0.46	44.17± 0.35	26.14±0.13	97.26±0.37
F3	248.3±0.4	1.4±0.06	3. 27± 0.31	0.33± 0.06	98.75	17± 0.76	38.16±0.21	21.12±0.21	98.75±0.38
F4	250.2±0.5	1.4± 0.04	3.15± 0.25	0.41 ±0.02	98.34	35 ±0.53	59.46±0.51	38.26±0.37	89.76±0.43
F5	249.5±0.6	1.4± 0.02	3.16 ± 0.13	0.28 ±0.06	98.45	27±0.72	55.16±0.29	35.18±0.31	94.89±0.34
F6	250.4±0,4	1.2±0.03	3. 19± 0.23	0.48± 0.04	99.24	25±0.51	49.14±0.37	31.12±0.11	96.19±0.45
F7	249.3±0.7	1.4±0.06	3.24± 0.37	0.36± 0.04	96.92	51±0.43	61.9±0.26	58.23±0.25	87.75±0.64
F8	248.2±0.5	1.4±0.08	3.17± 0.22	0.39±0.02	98.15	49±0.27	59.62±0.44	55.11±0.23	89.75±0.49
F9	250.5±0.6	1.3±0.07	3.21 ± 0.34	0.39±0.06	98.82	48±0.34	56.04±0.13	53.72±0.73	92.96+0.68

Values are expressed as Mean ±SD, n=3

In the present study Losartan potassium Mouth dissolving tablets were prepared by using superdisintegrants namely, crospovidone, crosscarmellose sodium and sodium starch glycolate. All the formulations were evaluated for various parameters like hardness, friability, drug content, wetting time, water absorption ratio, disintegration time and *In-vitro* drug release values are given in **Table No. 3 & 4**.

The hardness of the tablets was found to be 3.14 ± 0.02 to 3.27 ± 0.31 kg/cm^2 and friability was found to be below 1% indicating good mechanical resistance. The thickness of the tablets was found to be 0.28± 0.06 to 0.48± 0.04. All the tablets passed weight variation test, as percentage weight variation was within the pharmacopoeial limits i.e. ±7.5%. The drug content was found to be 98.02 to 98.75%, indicating uniform distribution of drug in the tablets & *in-vitro* drug release was found to be 87.75 ± 0.64 to 98.75 ±0.38

***In-vitro* dissolution study:**

The dissolution study on formulation no: F1 to F9 were carried out using 900 ml of respective dissolution medium as mentioned (**Table no: 5**) at 50rpm using USP. The formulations F1 to F9 showed 70.55 ± 0.83 to 98.75 ±0.61 in 10 min respectively. (Table no 14) the rapid *In-Vitro* dissolution was shown in the formulation F3 containing Crospovidone.

High dissolution resulted due to faster break down & rapid disintegration of tablet.the dissolution graphs are shown in fig 4.7-4.9. by this study an important coclusion can be drawn that addition of superdisintegrants technique has improved the dissolution profile of the water soluble drugs besides the disintegration time.

Drug release study by *in-vitro* drug dissolution

Table 5: Cumulative percentage drug release of formulations

Time (min)	Cumulative Percent Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	25.48±0.64	28.75±0.99	30.06±0.75	19.44±0.87	20.11±1.27	23.62±0.73	17.12±0.89	19.82±1.01	21.36±1.02
2	29.56±0.59	41.2±0.79	48.13±0.99	22.23±0.95	26.34±0.96	31.73±0.89	21.45±0.91	23.01±1.29	25.13±1.09
3	36.29±0.61	45.62±0.79	59.75±0.69	28.18±0.85	35.65±0.91	41.19±1.02	25.88±0.91	29.13±0.05	31.01±1.09
4	46.71±0.75	55.49±0.89	71.450.±0.97	35.62±0.89	42.01±1.21	46.12±1.59	31.29±0.99	35.15±0.09	37.11±1.31
5	51.76±0.06	59.32±0.98	79.21±1.09	46.62±1.25	49.92±1.09	58.72±1.09	41.82±0.96	44.52±1.59	48.82±1.11
6	58.12±0.093	71.81±0.85	85.16±1.05	51.56±1.29	56.43±0.96	64.28±0.96	51.66±1.07	56.25±1.14	58.08±1.17
7	61.46±0.78	76.51±1.52	89.14±0.86	55.91±0.54	61.14±0.62	69.38±1.26	54.19±0.69	58.35±1.99	61.42±1.91
8	77.19±0.96	79.11±0.89	93.25±0.65	59.89±0.52	65.23±1.06	81.42±0.58	61.45±1.09	65.41±1.94	70.38±0.
9	81.95±0.91	89.12±0.89	96.52±1.23	67.79±1.45	72.71±0.52	84.18±0.65	78.15±1.56	81.21±1.25	89.11±1.89
10	91.24±0.75	96.35±0.88	98.75±0.61	81.29±1.25	89.65±1.52	94.46±0.41	82.96±0.84	86.96±0.99	90.21±1.79

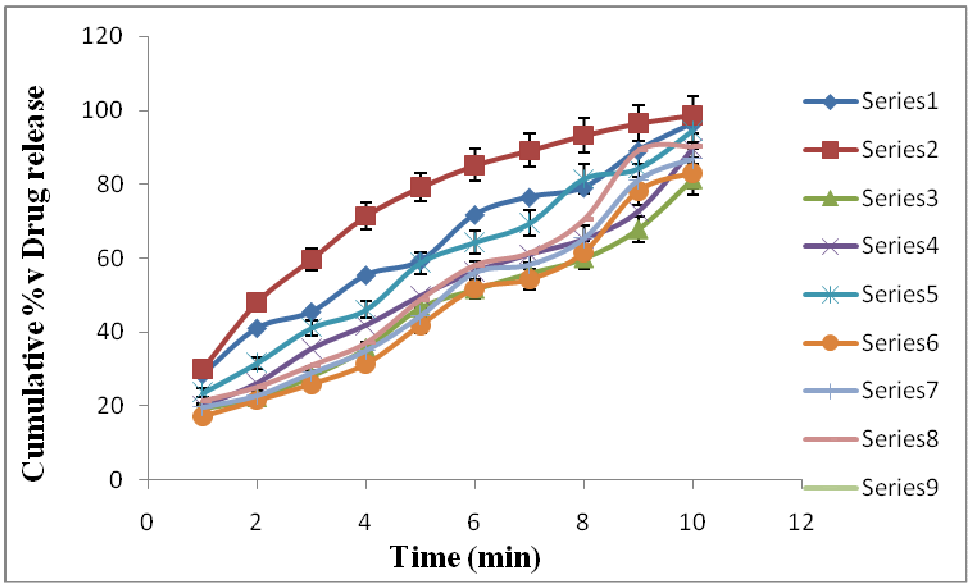

Figure 5: Cumulative percentage drug release of formulations

Table 6: Accelerated stability studies for optimized formulation (F3)

Parameters	Time in months			
	0 (Initial)	1st month	2nd month	3rd month
Hardness (kg/cm^2)	3.27±0.31	3.27±0.31	3.27±.0.31	3.26±0.21
Friability (%)	0.33±0.61	0.33±0.61	0.35±0.61	0.35±0.52
Disintegration time(sec)	17±0.76	17±0.76	17±0.76	18±0.82
Drug content (%)	99.75±0.027	99.75±0.027	99.75±0.015	99.80±0.011
***In-vitro* drug release (%)**	99.75±0.038	99.75±0.038	99.75±0.015	98.75±0.011

The stability of this optimized formulation (F3) was known by performing stability studies for three months at accelerated conditions of 40^0C ± 75 % RH on optimized formulation. The formulation was found to be stable, with no change in the hardness, disintegration time, drug content and *In- vitro* drug release pattern results are showed in T**able 6**.

Drug-excipients compatibility study by FTIR

FTIR study was done to verify if there was any interaction between the pure drug and various excipients were employed. The various FTIR graphs both of pure drug and optimization formula formulated into IR pellet and scanned.

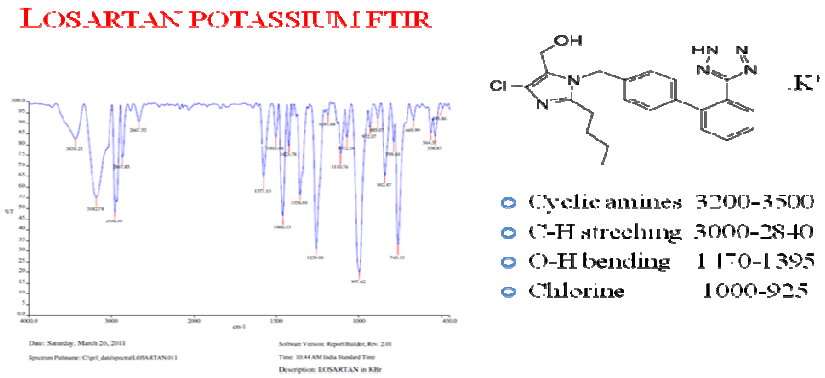

Figure 1: IR spectra of Losartan potassium

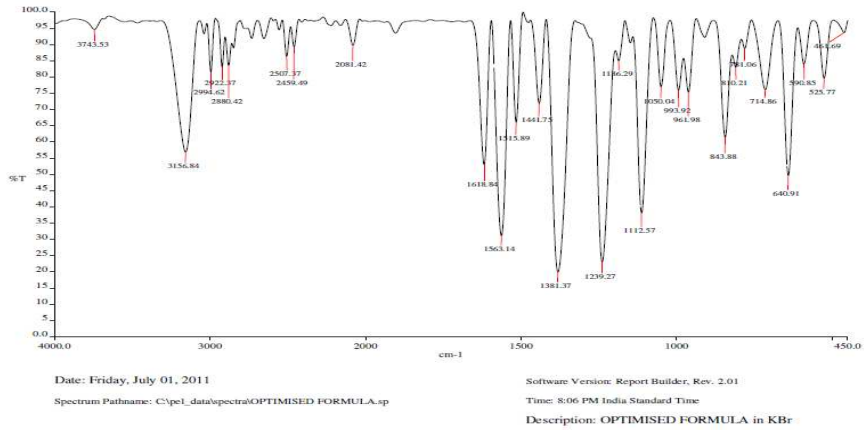

Figure 2: IR spectra of Optimized formulation F3

DSC Studies:

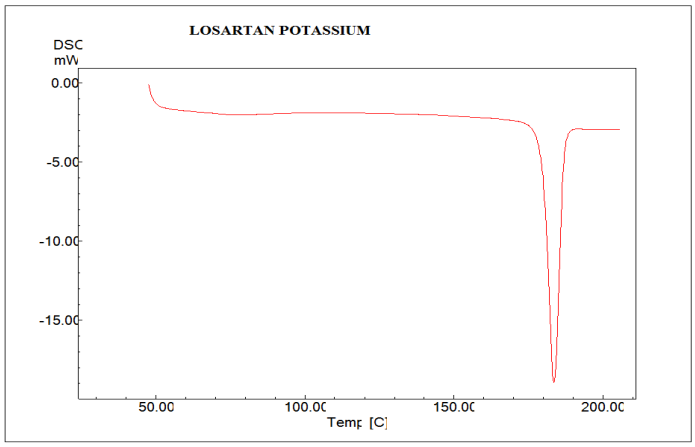

Figure 3: DSC thermogram of losartan potassium - pure drug

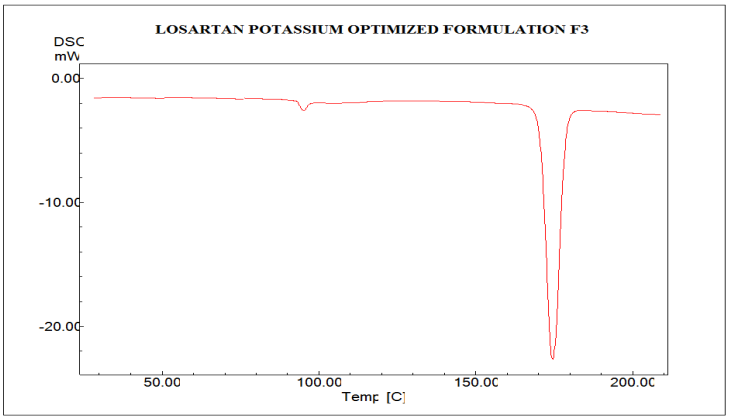

Figure 4: DSC Thermogram of optimized formulaiton (F3)

DSC thermograms revealed that there is no considerable change observed in melting endotherm of losartan potassium pure drug (184.97) and drug in optimized formulation (F3) (178.35). It indicates that there is no interaction takes place between drug and other excipients used in the formulation

CONCLUSION

Mouth dissolving tablets of Losartan potassium prepared by direct compression method

The *In vitro* drug release from formulation containing super disintegrant CP was found between 87.64±0.36 to 98.75±0.61 in 10 min and the maximum drug release was found with F3 formulation. The *In vitro* drug release from formulation containing superdisintegrant CCS was found between 85.69±0.73.34 to94.46±0.41 in 10 min and the maximum drug release with F6 formulation. The *In vitro* drug release from formulation containing superdisintegrant SSG was found between 82.48±1.06 to 90.21±1.79 in 10 min and the maximum drug release with F9formulation. Mouth dissolving tablets of Losartan potassium were prepared by using different superdisintegrants like crospovidone, croscarmellose sodium and Sodium starch glycolate by direct compression. Precompression parameters were conducted for all formulations blend and were found to be satisfactory. The prepared tablets were evaluated for various parameters like content uniformity, hardness, friability, wetting time, water absorption ratio, disintegration time and *In-vitro* dissolution. The results indicated that the tablets complied with the official specifications. The disintegration studies shown that the all formulations disintegrated in less than 1 minute, The formulation F3 shown less disintegration time of 17 seconds, the croscarmellose sodium and sodium starch glycolate shown more disintegration time than crospovidone, an accelerated stability study on optimized formulation was performed. The formulation was found to be stable, there was no change in the hardness, friability, disintegration time, and *In-vitro* drug release pattern.

DSC and FTIR data revealed that no interactions takes place between the drug and polymers used in the optimized formulation. In conclusion, it can be stated that the objective of the study has been achieved. From the above study the formula used for F3 formulation was concluded as an optimized formulation due to its less disintegration time and good % drug release when compared with other formulations.

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