IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
August 2016 Vol.:7, Issue:1

Design and Assessment of Losartan Potassium Oro-Dispersible Tablets Using Modernistic Versatile Co-Processed Superdisintegrants

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ISSN 2349-7203
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Submission: 5 August 2016
Accepted: 10 August 2016
Published: 25 August 2016

Keywords: ODT, Losartan Potassium, Co-processed superdisintegrants, Direct Compression Method

ABSTRACT

Co-processed excipient represents a convenient and economic way to develop new excipient functionalities. In the present investigation novel co-processed superdisintegrants were developed by solvent evaporation method using crospovidone and sodium starch glycolate in different ratios (1:1, 1:2 & 1:3) for use in the orodispersible tablets. In this new period of innovative drug delivery systems, the focus of drug formulators are oriented towards increasing the potency of existing drug molecule through these innovative approach to drug delivery. Losartan potassium is widely used as an antihypertensive drug, which is a potent drug candidate for developing into orodispersible tablets (ODTs). It has low bioavailability due to first pass metabolism. Hence the main objective of the study was to formulate orodispersible tablets of losartan potassium to achieve a better dissolution rate and further improving the bioavailability of the drug. Orodispersible tablets of losartan potassium were formulated by using different concentration of superdisintegrants like sodium starch glycolate, crosprovidone individually, physically mixed and co-processed and all the batches were prepared by direct compression using standard round faced punch on a sixteen station rotary (Cadmach, Ahmadabad) tablet punching machine. All the tablets were prepared & evaluated for various parameters like hardness, weight variation, friability, thickness, drug content, in vitro dispersion time, disintegration time, wetting time, water absorption ratio and dissolution time. Through all the formulations containing 4 % w/w of co-processed superdisintegrant (1:1 mixture of CP and SSG) was found to be shown rapid drug dissolution.

INTRODUCTION

Losartan potassium approved by the FDA in April 1995, Losartan was launched that month as the first non-peptide anti-hypertensive drug in the new class of Ang II receptor antagonists Losartan potassium is an antihypertensive drug belongs to the category of Angiotensin II receptor antagonist. Losartan potassium is extensively used as an antihypertensive drug, which is an effective drug candidate for developing into orodispersible tablets (ODT's). It has low bioavailability due to first pass metabolism. The drug is having the half-life of 1.5-2hrs, so orodispersible tablet formulation avoids the first pass metabolism& formulating it as an ODT causes rapid dissolution of drug & absorption, which may produce the rapid onset of action in the treatment of hypertension[1].

The esteem of solid dosage form coupled with compactness, flexibility, high-precision dosing and manufacturing skills make this dosage form ruling among all dosage forms. Oral drug delivery is a benchmark in pharmaceutical industry regarded as most invulnerable and efficient method with highest degree of patient compliance. The pioneering attribute of ODT furnishes ease of oral administration of medicament which facilitates faster drug dissolution in mouth in >60 sec. Orodispersible tablets allow high drug loading, good chemical stability and no chewing is needed. A novel orodispersible formulation may also be applied to deliver therapeutic agents through buccal mucosa directly to systemic circulation thereby avoiding the first pass metabolism adds an advantage.[2] Orodispersible tablets are not only designated for people who have swallowing complications but also are optimal for active people[3]. The main objective behind formulation of such a dosage form will be definitely countable.

There are hardly ever excipients which illustrate all the optimal characteristics required for direct compression. Excipients with amended performance can be obtained by developing

advanced chemical excipients, new grades of existing materials and new combination of existing materials. In order to overcome this problem there is a need to develop excipients with multiple characteristics built into them such as better flow, low/no moisture sensitivity, superior compressibility and rapid disintegration ability. One of the interesting options for such excipients development is co-processing. The method of Co-processing is based on the unusual concept of two or more excipients interacting at the sub particle level, the objective of which is to provide

an additive action of performance as well as concealing the unsuitable properties of individual, without interacting at chemical level[4].

In the present investigation, the preparation and evaluation of orodispersible tablets by using co-processed superdisintegrants containing crosprovidone and sodium starch glycolate was studied. The reasons for choosing the crospovidone are high capillary action, well-known hydration capacity and little affinity to form gels. Sodium starch glycolate was preferred because of its high swelling capacity. The perception of formulating ODT using co-processed superdisintegrants which increase the water uptake with shortest wetting time and thereby decrease the disintegration time of the tablets by direct compression technique. The study was designed to frame an oral delivery device, in the form of ODT by using direct compression technology, with the purpose of reaching a high serum concentration in a short period of time and examine the effect of different types of superdisintegrants on the release profile of the drug in the tablets and to improve patient compliance.

MATERIALS AND METHODS

Losartan potassium (Ipca Labs, Ratlam), Sodium starch glycolate, and crospovidone are obtained from DMV-Fonterra Excipients GmbH & Co. KG, Bengaluru as gift sample. Mannitol (CDH chemicals, New Delhi), Microcrystalline cellulose & Talc (LOBA Chemie, Mumbai), Colloidal silicon dioxide, Aspartame, Peppermint Flavor is purchased from S.D. Fine chem., Mumbai.

Characterization of Drug & Excipients

FT-IR Spectroscopy

It was employed to ascertain the compatibility between losartan potassium and the selected excipients. The pure drug and the drug with excipients were scanned separately .FT-IR spectrum of losartan potassium was compared with the FT-IR spectrum of losartan potassium with the excipients

Preparation of Physical Mixtures of superdisintegrant

The physical mixture of superdisintegrants i.e. crospovidone and sodium starch glycolate was prepared by simple trituration method in three different ratio's i.e. 1:1, 1:2, 1:3 up to 4% w/w .

Preparation of Co-processed excipients

The co-processed excipients were prepared by solvent evaporation method. A blend of excipient was added to 60 ml of isopropyl alcohol in 250 ml beaker. The contents of the beaker (250 ml capacity), were mixed thoroughly and stirred on a magnetic stirrer while maintaining the temperature between 50-60 ^{0}C till most of isopropyl alcohol has been evaporated. The wet coherent mass was granulated through # 60-mesh. The wet granules were dried in a hot air oven at 60^0 C for 20 minutes. The dried granules were sifted through # 60-mesh4.

Evaluation of Physical mixture & Co-processed mixture of superdisintegrants[5-10]

The prepared blends of physical and co-processed mixture were evaluated on the basis of flow property like bulk density, tapped density, angle of repose, carr's index and Hausner's ratio.

Evaluation of optimized Co-Processed mixture batch

Scanning Electron Microscopy (SEM Analysis)

The shape and surface topology of the crospovidone, sodium starch glycolate& co-processed mixture of sodium starch glycolate & crosprovidone of batch CM1 i.e. optimized batch of co-processed mixture (1:1) ratio were observed by SEM analysis(Zeiss-LEO 435VP, Orgon (USA)),after coating with gold, at different magnifications.

Particle Size Analysis

Particle size analysis of optimized batch of co-processed mixture CM1 was performed by Laser light scattering method at NIPER, Mohali by using Malvern Instruments Ltd. Three readings were performed for each measurement and Z-average (d.nm) was found out 2990.

Preparation of Losartan Potassium tablets[11-12]

ODT's were prepared by direct compression method by using the novel co-processed superdisintegrants, physical mixture of superdisintegrants and single superdisintegrants addition method. Tablets are compressed directly from powder blends of active ingredient and suitable excipients (including fillers, disintegrants, and lubricants) & then remaining excipients are added & tablet is compressed by rotary tablet compression machine (Cadmach, Ahmadabad, India).

Formulation chart

Ingredients (mg)	Formulation code				
	F_1	F_2	F_3	F_4	F_5
Losartan potassium	25	25	25	25	25
Sodium starchglycolate	-	8	-	-	-
Crosprovidone	-	-	8	-	-
Physical mixture (C.P. + S.S.G.)	-	-	-	8	-
Co-processed mixture (C.P.+S.S.G)	-	-	-	-	8
M.C.C.	40	40	40	40	40
Mannitol	121	113	113	113	113
Aspartame	6	6	6	6	6
Talc	4	4	4	4	4
Colloidal silicon dioxide	2	2	2	2	2
Peppermint flavor	2	2	2	2	2
Total	200	200	200	200	200

Where,

F_1: Control Batch (No Superdisintegrant)

F_2: Tablet formulation containing Sodium Starch Glycolate

F_3: Tablet formulation containing Crospovidone

F_4: Tablet formulation containing Physical Mixture of Superdisintegrants

F_5: Tablet formulation containing Co-processed Mixture of Superdisintegrants

Precompression study

The blend which is made into ODT by direct compression method was evaluated for bulk density, tapped density, angle of repose, carr's index & Hausner's ratio.

Evaluation of Losartan Potassium Tablets[13-16]

ODT's of losartan potassium was evaluated for weight variation, hardness,drug content, disintegration time, in vitro dispersion time, wetting time, water absorption ratio & dissolution studies.

Weight variation test:

Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average weight.

Drug content:

Twenty tablets were taken & powdered amount equal to 25 mg equivalent weight of drug was taken and dissolved in methanol, filter the solution and record the absorbance in UV spectrophotometer at 235 nm & drug concentration was measured using standard graphs.

Disintegration Time:

The disintegration time was determined in distilled water at 37 ±2 ^{0}C using disintegration test apparatus USP ED-2L (Electro lab, Mumbai).

Crushing Strength:

Hardness of the tablet was determined using the Monsanto hardness tester. The average values & standard deviation were calculated.

Wetting Time & Water Absorption Ratio:

Five circular tissue papers of 10 cm diameter are placed in a Petri dish with a 10 cm diameter, 10 ml of water-containing amaranth (a water soluble dye) is added to Petri dish, a tablet is carefully placed on the surface of the tissue paper, the time required for water to reach upper surface of the tablet is noted as a wetting time.

Water absorption ratio 'R' was determined using following equation:

$$R = 100 \times \left(\frac{W_a - W_b}{W_a} \right)$$

***In vitro* dispersion time:** Tablet was added to 10 ml of phosphate buffer solution of pH 6.8 (pH of saliva) at 37± 0.5^0C. Time required for complete dispersion of tablet was measured.

Dissolution studies: Dissolution studies for ODTs were performed in pH 6.8 phosphate buffer using USP Dissolution test apparatus (Electrolab, Mumbai, India) with a paddle stirrer. The dissolution medium was maintained at a temperature of 37± 0.5^0C. and samples were withdrawn at an interval of 5 min The withdrawn samples were filtered and absorbance was measured at 235nm using UV-visible spectrophotometer. Drug concentration was calculated from the standard calibration curve and expressed as cumulative percent drug dissolved.

RESULTS AND DISCUSSION

Drug excipient compatibility study

FTIR study: Identification of drug was done by FTIR spectroscopy.The infrared spectral assignment of Losartan potassium was obtained by FTIR (Jasco-470 plus), which shows the characteristic peaks of various functional groups of drug which matches with the standard spectra of drug.

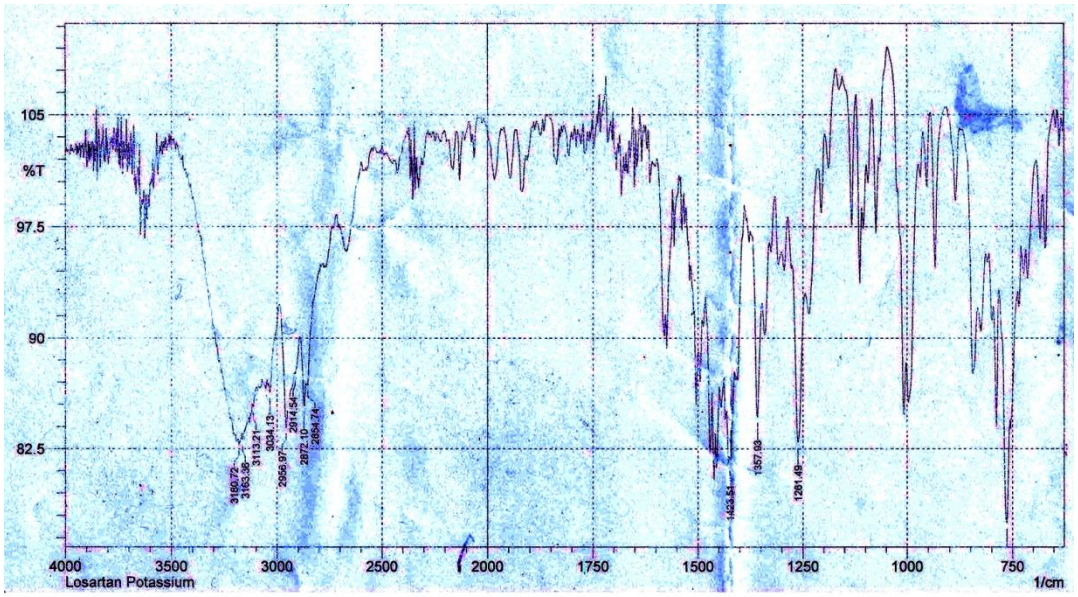

Figure 1: FTIR of pure drug

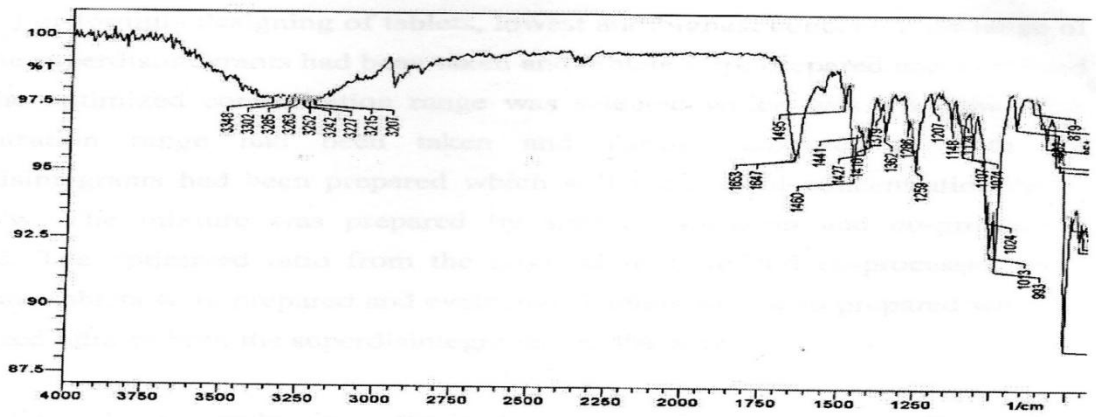

Figure 2: FTIR of Optimized Formulation

Table 1: Pre-compression parameters of optimized physical mixture and co-processed excipients

Parameters	Formulation code PM_1CM_1	
Bulk density (g/cc)	0.46	0.22
Tapped density (g/cc)	0.55	0.25
Angle of Repose (degree)	31.14	24.01
Carr's Index (%)	16.36	12.00
Hausner's Ratio	1.19	1.13

Evaluation of co-processed excipients

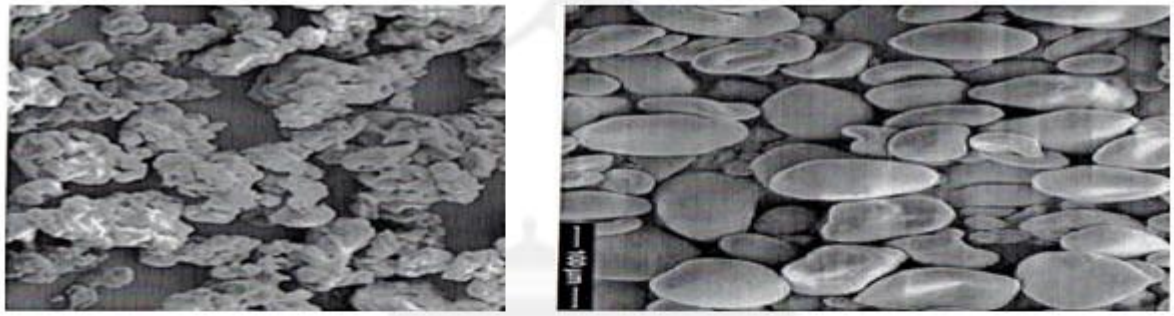

Figure 3: SEM photograph of sodium starch glycolate & crospovidone

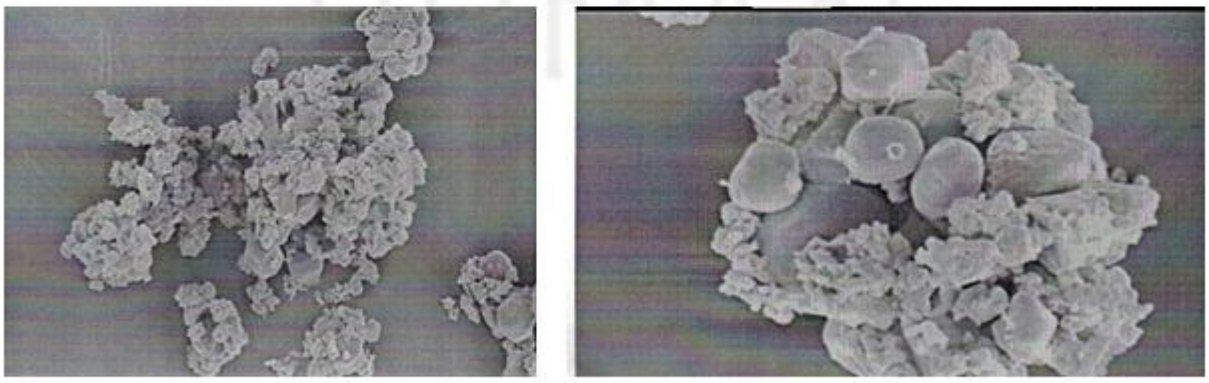

Figure 4: SEM Photograph of Co-Processed Mixture of Crospovidone & SSG

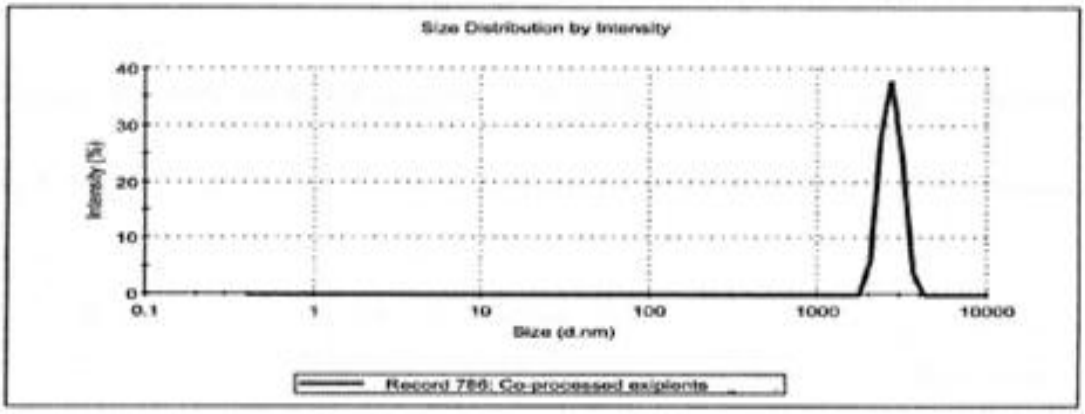

Figure 5: Particle size determination of co-processed blend

Table 2: Pre-compression Parameters of Powder blend

Parameters	Formulation code				
	F_1	F_2	F_3	F_4	F_5
Bulk Density (g/cc)	0.42	0.49	0.42	0.49	0.28
Tapped Density (g/cc)	0.52	0.67	0.51	0.57	0.32
Angle of Repose(degree)	33.50	32.78	31.9	29.01	20.00
Carr's Index (%)	19.2	18.0	17.6	15.02	11.08
Hausner's Ratio	1.23	1.19	1.18	1.15	1.14

Precompression Evaluation of the Powder Blend:

The powder blend is evaluated for different parameters and bulk density values are found to be 0.28 -0.42, tapped density values are 0.32-0.67s, % compressibility values are11-19,angle of repose values 20^0 -33^0. All the reported values are within standards, it means all the powder blends have good flow properties.

Table 3: Post-compression parameters of ODT of Losartan Potassium

S.No	Parameters	Formulation code				
		F_1	F_2	F_3	F_4	F_5
1	**Weight Variation(mg)**	202.22±1.1	201.72±1.73	201.01±1.20	200.89±1.35	200.22±1.45
2	**Hardness(kg/cm2)**	2.86 ± 0.05	3.0 ± 0.07	3.1 ± 0.2	3.12 ± 0.15	3.14 ± 0.04
3	**Friability(%)**	0.71 ± 0.017	0.67 ± 0.021	0.64 ± 0.028	0.57 ± 0.03	0.55 ± 0.035
4	**Thickness (nm)**	2.89±0.02	2.91±0.04	2.91±0.03	2.87±0.02	2.88±0.04
5	***Invitro*Dispersion Time (sec)**	131 ± 2.70	70.14 ± 1.90	53.18 ± 1.69	41.99 ± 1.45	22.16 ± 0.55
6	**Wetting Time (sec)**	141 ± 2.54	80.03 ± 2.15	63.36 ± 1.88	44.27 ± 0.62	24.22 ± 0.81
7	**Water Absorption Ratio (%)**	45.81 ± 3.60	60.51 ± 2.93	75.34 ± 1.96	87.12 ± 1.83	90.84 ± 1.41
8	**Disintegration time(sec)**	107.333 ± 2.35	57.916 ± 2.0	47.49 ± 1.81	38.39 ± 1.31	20.27 ± 1.42
9	**Percent Drug Release(%)**	10.9±1.84	72.260±3.3	89.67±1.47	94.08±1.65	99.690±1.592
10	**Drug Content(%)**	95.56 ± 0.370	96.48 ± 0.419	97.98 ± 0.469	98.00 ± 0.520	98.99 ± 0.572

The prepared ODT of losartan potassium were evaluated for weight variation, hardness, friability, thickness, disintegration time, *in vitro* dispersion time, wetting time, water absorption

ratio, % drug content and *in vitro* drug release studies. Hardness values of prepared were in between 2.86-3.14 kg/cm^2. Weight variation values are in-between 200-202 mg. Friability values were in the range of 0.5-0.7%, thickness values are in between 2.88-2.91, Percentage Drug contents values were found to be in the range of 95-99%. All evaluated parameters values are found to be within limits.

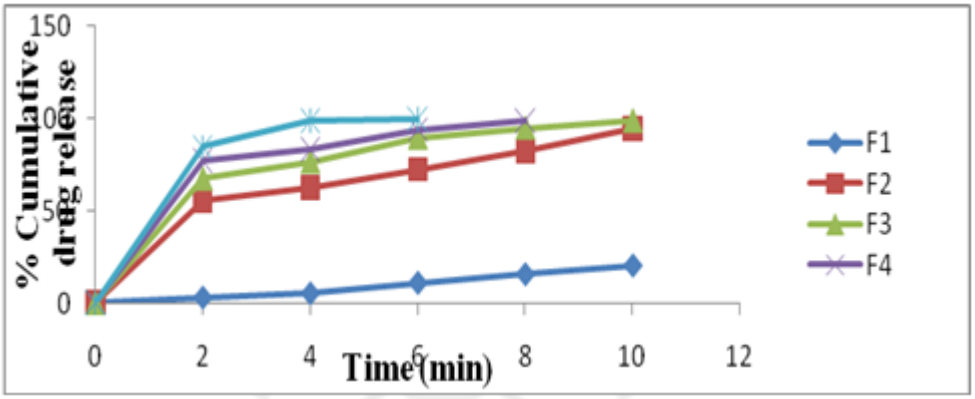

Figure 6: Cumulative Percent Drug Release of Various Formulations

In vitro drug release is conducted by USP II Paddle apparatus. It was performed in 900 ml phosphate buffer pH 6.8 using USP type II (paddle) apparatus at 50 rpm for 15 minutes (37 ± 0.5^{0}C). Aliquots of the dissolution medium (5 ml) were withdrawn at specific time intervals. The % cumulative drug release graph showed that the among all batches prepared batch F_5showed the best results among all the batches, as it released drug 99.690 % in 6 min, as this batch contains co-processed excipients of superdisintegrants sodium starch glycolate and crospovidone (4%).it was found out that the batch F_5 also showed short disintegration and wetting time of 20.27 sec &24.22 sec which means rapid onset of action as compared with the other prepared formulations. the other parameters like % drug content, water absorption ratio & *in vitro* dispersion time of batch was also best when compared with other batches, thus batch F_5 was selected as optimized formulation.

The stability study of formulations was carried out according to the ICH guidelines for zones III and IV. The formulations were stored at 40 ± 2^{0}C/75 ± 5% RH for 3 months by storing the samples in a stability chamber. At the end of 3 months tablets were tested for hardness, drug content and disintegration. In-vitro dissolution was carried out for selected formulation.Samples

were withdrawn at an interval of 7 days for 3 months and were studied for *in- vitro* drug release, drug content uniformity and disintegration time.

On the basis of stability study of optimized formulation i.e. F5 of co-processed superdisintegrants it was concluded that there is no significant change in parameters like drug content, drug release and disintegration time, therefore, optimized formulation was found to be stable.

CONCLUSION

From the present work, it was concluded that orodispersible tablet of losartan potassium can be prepared by direct compression using novel co-processed superdisintegrants which impart rapid action, increased bioavailability. The formulation of ODT of losartan potassium has been found to be capable of overcoming the gastric side effects associated with the drug and also imparts rapid drug release by avoiding hepatic first pass metabolism which was shown *in vitro* drug release profile. The result of evaluation parameters suggested that co-processed mixture of crospovidone and sodium starch glycolate in the 1:1 ratio (4%) w/w was best to generate efficacious ODTs as compared with the simple physical mixture and individual added superdisintegrant in the same ratio. The SEM analysis of excipients also revealed that there is only physical entanglement of existing excipients which can lead to synergism of all functional properties/

The advantages of our new ternary phase superdisintegrants are easy adaptability, economically in industry and the possibility of bypassing the existing patents in the areas of quick disintegration and dissolution. Development of new excipient requires safety evaluation which is expensive and time consuming. Instead of developing new excipient, coprocessing of existed approved excipients will reduce the safety evaluation.

Thus ODT of losartan potassium will be beneficial for patients and can be regarded as novel approach as compared with the conventional dosage forms of drug available in market. Undoubtedly the availability of various technologies and the manifold advantages of orodispersible tablets will surely enhance the patient compliance, low dosing, and rapid onset of action, increased bioavailability, low side effect, good stability, and its popularity in the near

future. Orodispersible tablet of losartan potassium will open new business opportunity like product differentiation, product promotion, patent extension and life cycle management

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