ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Formulation Development and Evaluation of Orally Disintegrating Tablets of Losartan Potassium by Direct Compression Method

Jagadale Sachin K,* Patil Pradeep S and Navale Rajini.

Marathwada Mitra Mandal's College of Pharmacy, Thergaon (Kalewadi), Pune-4110 33, Maharashtra, India.
R.C.Patel Institute of Pharmaceutical Education and Research, Shirpur, Dhule:-425405, Maharashtra, India.

ABSTRACT

In the present work, mouth dissolving tablets of losartan potassium were design with a view to enhance the Patient compliance and provide a quick onset of action. Losartan potassium is an angiotensin receptor antagonist, used in the management of hypertension. It has low bioavailability due to its first pass metabolism. Hence the main objective of the study was to formulate mouth dissolving tablets of Losartan potassium to achieve a better dissolution rate and further improving the bioavailability of the drug. Mouth dissolving tablets prepared by direct compression and using super disintegrants like Tulsoin-335 and Tulsion-339 in different concentration and evaluated. The prepared batches of tablets were evaluated for hardness, weight variation, friability, disintegration time and in-vitro dissolution profile and found satisfactory. Among all, the formulation F3 containing Tulsion- 335 in 4% amounts was considered to be best formulation, which showed complete release within 5 min. In the present work, mouth dissolving tablets of Losartan potassium were designed with a view to enhance the patient compliance by using Tulsion-335.

Keywords: Losartan Potassium, Orodispersible Tablets, Tulsion-335.

**** Corresponding author***

ISSN: 0975-8585

INTRODUCTION

Difficulties with and resistance to tablet-taking are most common in all patient groups and can exacerbate compliance problems and undermine treatment efficacy. Physical problems with swallowing (dysphasia) can occur at any age but are particularly prevalent in the elderly and those with dementia, whereas refusal to swallow is often encountered in geriatric, pediatric and psychiatric patients. Nonetheless, oral dosing remains the preferred mode of administration for many types of medication due to its simplicity, versatility, convenience and patient acceptability. In recent years, rapid-dissolving oral drug formulations have been developed to overcome problems related to swallowing difficulties [1-4].

Fast onset of action is a major concern in the treatment of hypertension. The problem of slow onset of action of drugs can be overcome by development of an appropriate dosage form. Fast disintegrating in mouth tablets are best suited and have gained popularity in the recent years in oral antihypertensive drug therapy. This new formulation of antihypertensive drugs can offer advantages over older formulation in terms of convenience, side-effect profiles, efficacy, and/or a fast onset of action [5].

Losartan Potassium is an antihypertensive drug belongs to the category of Angiotension II receptor antagonist. The molecular weight of Losartan Potassium is 461.01g/mol, half life is 1.5 to 2hr, and its bioavailability is 25%-35%, metabolized mainly in the liver. FDTS are soluble in saliva are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into stomach, thus enhance the bioavailability by avoiding first pass metabolism.

FDTS also leads to an increased patient compliance, and fast onset of action. Keeping all these factors in mind, it was considered appropriate to formulate FDTS of Losartan Potassium. The literature survey reveals that Losartan Potassium is a promising drug candidate for FDTS formulation [6].

MATERIAL AND METHODS

Losartan Potassium was procured from Zim laboratories, Nagpur, Tulsion-335 and Tulsion-339 were a kind gift from Thermax India Pvt Ltd. Microcrystalline cellulose, Sodium Saccharin, Mannitol, Sodium Bicarbonate, Tartaric acid, Magnesium Sterate and Talc were gifted from Oswal chemicals Pune. All other reagents used were of analytical grade.

EXPERIMENTAL

UV spectral characterization

Literature survey revealed the availability of the UV method with spectrophotometer detection for routine quantitative analysis in pharmaceutical dosage form for Losartan this method was adopted for the determination of Losartan potassium.

Standard stock solutions having 100µg/ml Losartan potassium were prepared by dissolving 10 mg of drug in phosphate buffer pH 6.8. Appropriate dilutions were made for

drug from the standard stock solution and the solutions were scanned in the wavelength range of 400-200 nm. The absorption spectra were thus obtained.

Construction of calibration curve

Standard stock solutions having 100µg/ml Losartan potassium were prepared by dissolving 10 mg of drug in phosphate buffer pH 6.8. The standard solutions were prepared in the concentration range of 2-20 µg/ml by diluting stock solution with phosphate buffer pH 6.8. The solutions were scanned for λ_{max} on UV-Visible Spectrophotometer in the wavelength range of 200-400 nm. Then these solutions were analyzed at the λ_{max} 225nm. The calibration curve of absorbance v/s concentration was plotted. Data was subjected to linear regression analysis. The linearity range was found to be 2-20 µg/ml with correlation coefficient 0.998.

FTIR spectra

Losartan potassium was mixed with IR grade potassium bromide. This sample was scanned in the range of 400-4000 $^{cm-1}$ in Jasco FTIR 4100 and the IR spectra observed.

Formulation of Orodispersible tablets

All the ingredients (Table 1) were passed through mesh no 60 and they were mixed together in Mortar and pestle for 15 minutes. Talc and Magnesium Sterate were mixed at the end of the process.

Table 1: Formulation of Orodispersible tablets of Losartan Potassium.

Ingredients	F1 Mg	F2 Mg	F3 Mg	F4 Mg	F5 mg	F6 Mg
Losartan potassium	25	25	25	25	25	25
Mannitol	79	77	75	79	77	75
Microcrystalline cellulose	45	45	45	45	45	45
Sodium bicarbonate	24	20	28	24	20	28
Tartaric acid	16	20	12	16	20	12
Magnesium state	3	3	3	3	3	3
Talc	2	2	2	2	2	2
Tulsion-335	4	6	8	-	-	-
Tulsion-339	-	-	-	4	6	8
Total	200	200	200	200	200	200

Evaluation of Orodispersible tablets of Losartan

Precompression Parameters

Angle of Repose *(θ)*

Angle of repose is defined as the maximum angle possible between the surface of a pile of the Powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose.

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

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

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

Bulk Density

Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another.

LBD = Weight of the powder --------- (a)
Volume of the packing
TBD = Weight of the powder ---------- (b)
Tapped volume of packing

Carr's Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index.

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

Hausners Ratio

It is determined by comparing tapped density to the bulk density by using following equation

$$\text{Hausners ratio} = \text{tapped density / bulk deksity.}$$

The results of the powder flow properties determination are summarised in table no 17

Evaluation of Tablet Properties

Uniformity of Weight [7]

The test was performed according to specifications given in the Ph. Eur., 2004 on 20 tablets. The maximum acceptable limit is ±7.5% deviation of an individual mass from average mass.

Measurement of Tablet Friability [8]

Tablet friability was measured using the Roche Friabilator according to Ph. Eur, on ten tablets each. The friability was determined as the mass loss in percent according to Eq

$$F= W_A-W_B/W_A .100$$

Where f—Friability, WA—Initial weight (g), WB—Final weight (g). Tablets of friabilities under 1% are acceptable .

Measurement of Tablet hardness

The crushing strength of tablets was measured by a Monsanto Hardness Tester[9]

Wetting Time [10]

A piece of tissue paper was folded twice and placed in small petri dish containing 6 ml of phosphate buffer (pH 6.8) the tablet was placed on it and the time required for complete wetting of tablet was recorded.

Water Absorption Ratio [11]

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 was allowed for complete wetting. The wetted tablet was then weighed. Water absorption ratio, R, was determined using following equation

$$R= (W_A-W_B) /W_B *100$$

Where, W_B—Weight of tablet before water absorption, W_A— Weight of tablet after water absorption.

***In-Vitro* Disintegration Time**

***In Vitro* Disintegration Time (DT) Using Petri Dish Method**

The *In- vitro* disintegration time of the orally disintegrating tablets was determined following the procedure described by Gohel et al (2004)[12]. 10 mL of water at 37 ^{0}C was placed in a petri dish of 10 cm diameter. The tablet was then carefully positioned in the center of the petri dish and the time required for the tablet to completely disintegrate into fine particles was noted. Measurements were carried out in replicates of three tablet (n=3) and mean were recorded.

***In Vitro* Dissolution Study**

Losartan Potassium tablet test conditions for the dissolution rate studies were used according USP specifications using USP 24, type II apparatus. The dissolution medium was

ISSN: 0975-8585

900 ml of Phosphate Buffer (PH6.8). The temperature of the dissolution medium and the rate of agitation were maintained at 37±0.5°C and 50 rpm, respectively. Aliquots of 5.0 ml of the dissolution medium were withdrawn at specific time intervals and the volume replaced by fresh dissolution medium, pre-warmed to 37±0.5°C. The drug concentration was determined spectrophotometrically at 225 nm using UV spectrophotometer (shimadzu 1800).

RESULT AND DISCUSSION

FTIR

Reference spectra of Losartan Potassium as per IP 2007

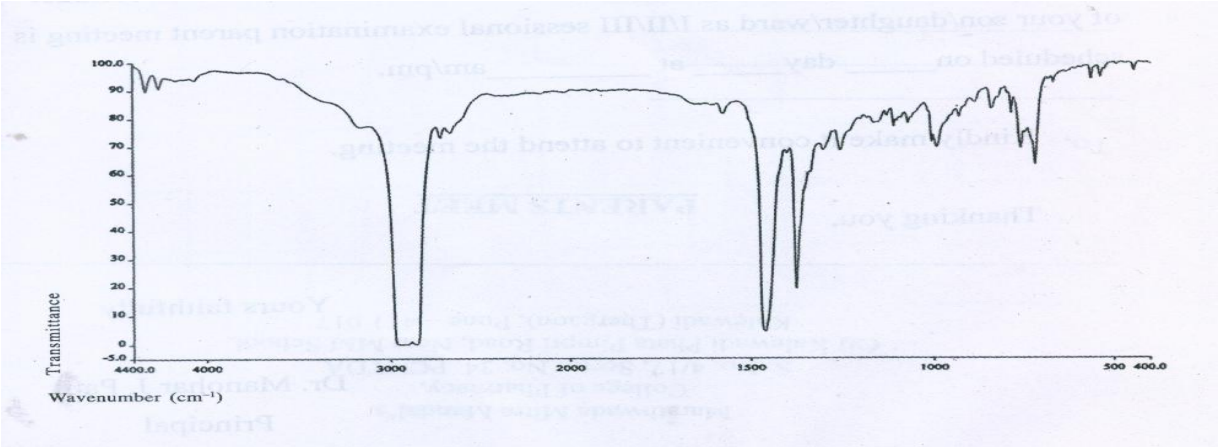

Figure 1: Reference spectra of Losartan PotassiumIR spectra of Losartan Potassium

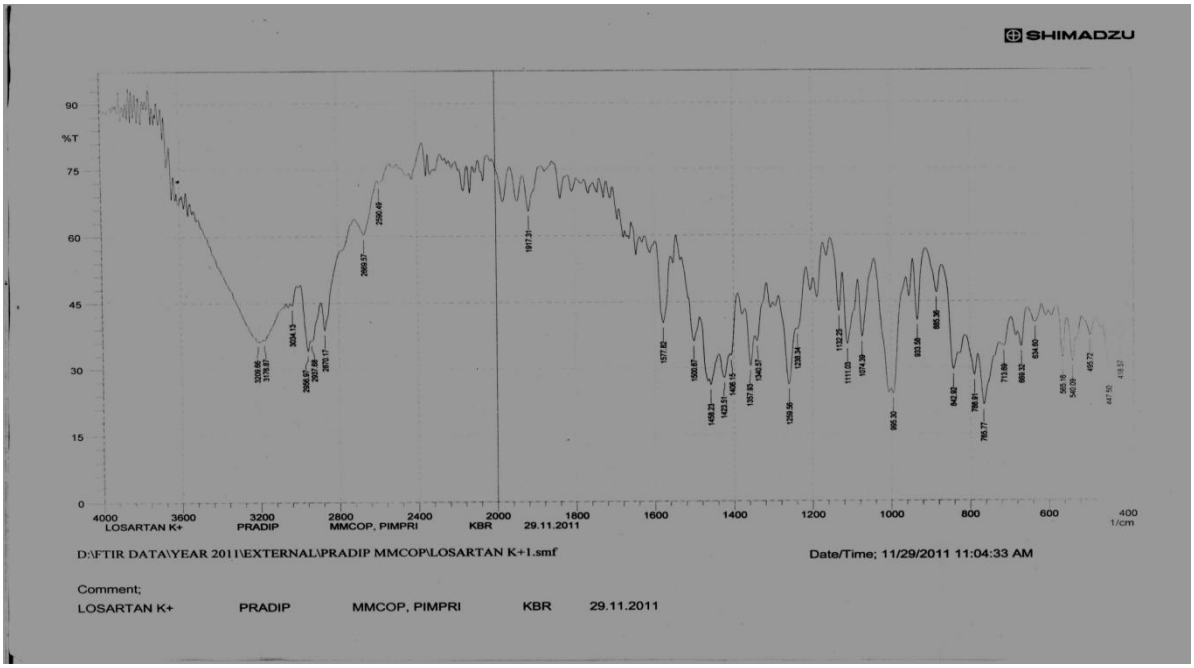

Figure 2: Obsreved IR spectra of Losartan Potassium

ISSN: 0975-8585

Table 2: Functional group and their value

Sr.NO.	Functional Group	Standard Value (nm^{-1})	Observed value (nm^{-1})
1	Chloride	785-540	765
2	Aromatic ring (stretch)	3150-30500	3034.13
		1600-1475	1577.82
3	Aromatic ring	Medium to strong absorption in region 1600-1451	1600-1450/m^{-1}
4	C-H-O	Bendig at 1440-1220	1440-1220cm^{-1}

UV SPECTRAL CHARACTRIZATION OF DRUG

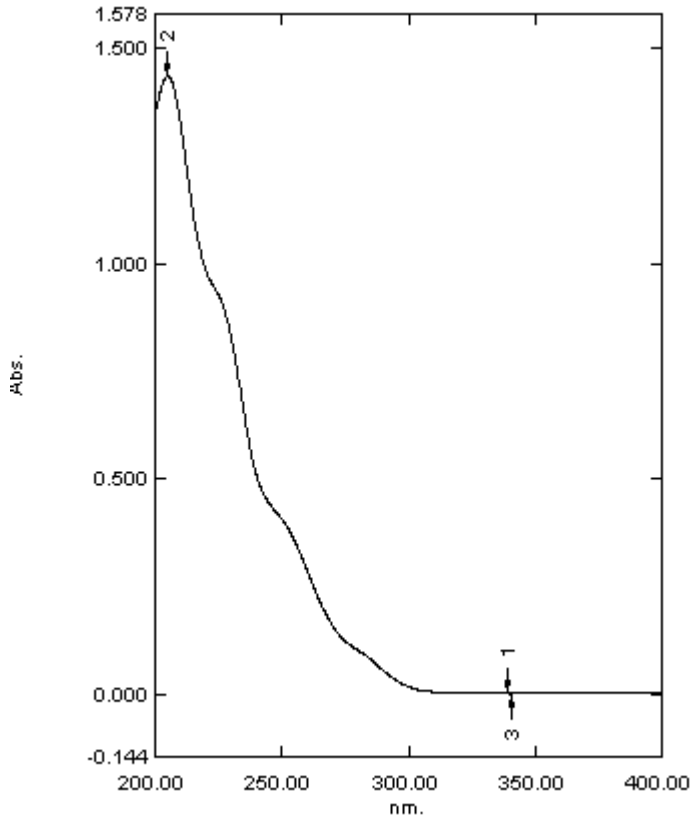

Figure 3: Determination of λ_{max} of Losartan Potassium

Scanning the appropriate solutions at 200-400nm showed the maximum absorption (λ_{max}) at 225nm. Therefore, 225nm is taken as (λ_{max}) for further study.

Calibration curve

The standard solutions were prepared in the concentration range of 2-20 µg/ml by diluting stock solution with phosphate buffer pH 6.8. The solutions were scanned at λ_{max} 225 nm and absorbances were recorded. The calibration curve of absorbance v/s concentration was plotted. Data was subjected to linear regression analysis. The linearity range was found to be 2-20 µg/ml with correlation coefficient 0.998.

ISSN: 0975-8585

Table 3: Calibration curve readings

Concentration(µg/ml)	Absorbance
2	0.165
4	0.269
6	0.373
8	0.503
10	0.655
12	0.826
14	0.915
16	1.035
18	1.165
20	1.301

From these reading calibration curve was plotted which shown in following figure. No. 4

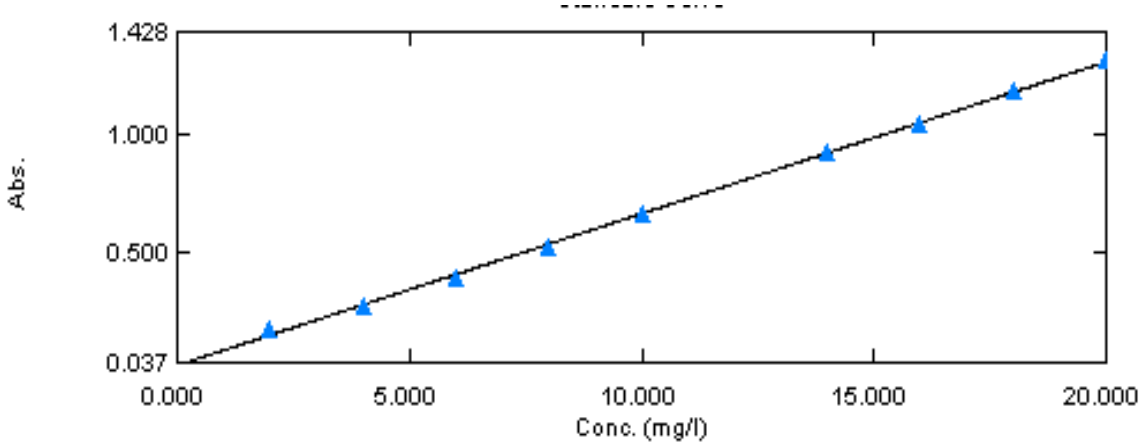

Figure 4: Calibration curve for Losartan potassium at 225nm

Standard regression equation: - y=0.065x + 0.020
R^2 :- 0.998

Table 4: Evaluation of precompression parameters

Sr.no	Formulation	Angle of repose	Bulk density	Tap density	Carr's index	Hausner's ratio
1	F_1	26.56	0.53	0.61	13.11	1.15
2	F_2	25.97	0.51	0.58	12.06	1.13
3	F_3	24.77	0.50	0.58	13.79	1.16
4	F_4	25.27	0.51	0.60	15.00	1.17
5	F_5	23.19	0.55	0.64	14.22	1.16
6	F_6	24.10	0.53	0.60	11.66	1.13

The powder flow properties were analyzed. It was observed that all formulations showed good flow properties with Carr's index ranging from 11.66 to 15.00 and Hausner's ratio below 1.25 which indicated good compressibility and flowability.

The disintegration time was measured using a petri plate method as described above. F3 formulation shows least disintegration time with an average of 22.5sec. It was observed that tablets containing 2%, 3 % and 4% of Tulsion-335 showed lesser disintegration time when compared with Tulsion-339 at the same concentration levels. All

the batches showed complete drug release within five minutes. Thus it was concluded that F_3 batch containing 4 % of Tulsion -335 showed good In-Vitro disintegration time as well as complete drug release within 5 minutes.

Table 5: Evaluation of Post Compression Parameters

Sr.no	Formulation	Uniformity of weight	Friability %	Hardness Kg/cm^2	In-vitro disintegration time (Sec)	In-Vitro % drug release Q_{T5}
1	F_1	Passes	0.73	3.6	85±0.94	99.35±0.70
2	F_2	Passes	0.65	3.8	37±1.24	100.90±1.8
3	F_3	Passes	0.46	3.5	22±0.47	100.63±0.65
4	F_4	Passes	0.38	4.2	71±1.24	100.3±1.8
5	F_5	Passes	0.43	3.6	96±0.94	100.4±1.4
6	F_6	Passes	0.49	3.2	29±1.24	101.29±0.7

CONCLUSION

From the evaluations we found that F_3 Batch of orodispersible tablets of Losartan Potassium containing 4 % of Tulsion- 335 gave the best disintegration time and also complete drug release within 5 minutes. It was thus concluded that Tulsion- 335 can be an effective Superdisintegrant in conc of 4 %.

REFERENCES

[1] Kennerley J. Int J Pharm 1987; 40(1–2): 119–123.
[2] Sandipan Kundu, P. K. Sahoo, Pharma Times April 2008;40: 4
[3] Kucherkar BS, Badhan AC and Mahajan HS. Phrma Times 2003;35:3-10.
[4] Kaushik D, Dureja H and Saini TR. Indian Drugs 2004; 41: (4) 187-193.
[5] Debjit Bhowmik, Chiranjib.B, Krishnakanth, Pankaj, R.Margret Chandira. Journal of Chem and Pharml Research, 2009;1(1): 163-177
[6] Jain CP, Naruka PS. Int J Pharmacy Pharm Sci 2009;1:219-226.
[7] Uniformity of mass of single dose preparations. European pharmacopoeia, 233 (2004).
[8] Bradoo R. JAMA India 2001; 4 (10):27-31.
[9] B Yunxia, Y Yorinobu, D Kazumi and O Akinobu. Chem Pharm Bull 1996;44(11): 2121-2127.
[10] MC Gohel, G Bansal and N Bhatt. Pharma Bio World 2005;3:75-80.
[11] Gohel M, Patel M, Amin A, Agrawal R, Dave R, Bariya N. AAPS PharmSci- Tech 2004; 5(3):36.