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International Journal of Pharmaceutical Sciences and Drug Research
2017; 9(5): 234-239

Research Article

ISSN: 0975-248X
CODEN (USA): IJPSPP

Formulation & Evaluation of Mouth Dissolving Tablets Containing Losartan Potassium Using Natural Superdisinigrants

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ABSTRACT

Losartan potassium is used as an antihypertensive drug but it goes under first pass metabolism due do which it has low bioavailability. Fast onset of action is major concern in the management of hypertension. Therefore the aim of this study is to formulate mouth dissolving tablet of losartan potassium to improve its bioavailability, to achieve fast onset of action and increase patient compliance. Mouth dissolving tablets were prepared by direct compression method using natural super disintegrating agents (banana powder & apple pectin) and evaluated for pre-compression parameters and post compression parameters such as appearance, dimensions, hardness, weight variation, friability, wetting time, dispersion time, water absorption ratio, disintegration & dissolution study. According to results of optimized batches it has been concluded that formulation batch F9 was an ideal batch which contain banana powder (2.5%) & cross povidone (2.5%) showed least disintegration time that is 26 seconds & maximum drug release of (99.68%) within 12 minutes and was best among all the formulations.

Keywords: Losartan potassium, mouth dissolving tablets, super disintegrating agent banana powder & apple pectin.

DOI: 10.25004/IJPSDR.2017.090506 **Int. J. Pharm. Sci. Drug Res. 2017; 9(5): 234-239**

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Received: 02 August, 2017; **Revised:** 23 August, 2017; **Accepted**: 24 August, 2017; **Published:** 15 September, 2017

INTRODUCTION

In spite of various route of drug administration the oral route of drug administration is the easiest, most suitable and mostly used route of drug administration for systemic effects. However it is presumed that 90% of drugs which are used for systemic effects are administered through the oral route of drug administration. [1] The oral dosage forms require water for drug administration and when there is no water available then patient trouble. Many patient find difficulty to swallow tablet and hard gelatin capsule, consequently they do not take medication as

prescribed. It is estimated that 50% of the population is affected by this problem which result high incident of incompliance and ineffective therapy. The difficulty is experienced in particular by pediatric and geriatric patients, but it also applied to people who are ill in bed and those active working patients who are busy or traveling, especially those who have no access to water. For these reasons, tablets which can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Rapidly dissolving ordisintegrating tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people. [2-5]

United States Food and Drug Administration (FDA) defined MDT as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue". The disintegration time for mouth dissolving tablets generally ranges from several seconds to about 3 minutes. [6-7]

Due to the presence of superdisintegrants, it gets dissolved quickly, resulting in rapid absorption of drug which results rapid onset of action. In mouth dissolving tablets the absorption is taking place directly from mouth that why do not suffers from the first pass metabolism, so bioavailability of drug increases. [8]

Losartan Potassium is an angiotesion II receptor antagonist and used as antihypertensive drug. The molecular weight of Losartan Potassium is 461.0 g/mole, half-life is 1.5 to 2 hours, and its bioavailability is 25-35%. It gets metabolized mainly in the liver. Mouth dissolving tablets are soluble in saliva are absorbed from the mouth, pharynx and esophagus as the saliva passes down into stomach, thus enhance the bioavailability by avoiding first pass metabolism. Mouth dissolving tablets also leads to an increased patient compliance, and fast onset of action. [9] Keeping all these factors in mind, it was considered appropriate to formulate mouth dissolving of Losartan potassium.

MATERIALS AND METHODS

Losartan potassium was received as a gift sample from Sun Pharma Ltd, Banana, apple and mixed fruit flavor was purchased from local market, MCC was taken from pharmaceutics laboratory which was purchased from Molychem Ltd, Aspartame, zinc stearate and cross povidone were obtained from pharmaceutics laboratory & were purchased from Lobachem, HPMC was obtained from pharmaceutical chemistry laboratory which was purchased from Qualikems. SLS was taken from main store and it was purchased from Central Drug House P. Ltd.

Preparation of Fast Dissolving Tablet

Fast dissolving tablets containing 25 mg of Losartan potassium were prepared by direct compression method using formula give in Table 1. The drug and excipients were passed through 60 mesh sieve ensure better mixing. Avicel and mannitol was used as a directly compressible diluent. The directly compressible mixtures were compressed using multi punch tableting machine fitted with 8 mm flat punches. Before compression, the surface of die and punch were lubricated with zinc stearate. [10]

EVALUATION

Pre-compression Parameters [11-12]

Angle of repose

Angle of repose is defined as the maximum angle possible between the surface of a pile of the Powder and horizontal plane. The improper flow of powder is due to frictional force between the particles and these frictional forces are quantified by angle of repose.

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

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

Where, θ = angle of repose; h = height of pile; r = 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 cohesiveness of particles.

Mathematically it is defined as:

$$\text{Bulk Density } (\rho_b) = w/V_b$$

Where, w = mass of powder; V_b= bulk volume

Tapped Density

Tapped density is defined as the mass of a powder divided by the tapped volume. It was determined by mechanically tapping the measuring cylinder and the volume was noted.

$$\text{Tapped density } (\rho_t) = w / V_t$$

Where, w = mass of powder; V_t = bulk volume

Carr's Compressibility Index

It is also one of the simple methods to evaluate flow property of a powder by comparing the bulk density and tapped density. It is calculated by

$$\text{Carr's Index} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Bulk Density}}$$

Hausner's Ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

Hausner's ratio = Tapped density/Bulk density

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

Post Compression Parameter [13-17]

Appearance

Twenty tablets of each formulation were taken to check any physical or surface roughness in the tablet formulation.

Dimension

Thickness and diameter were measured using a calibrated barmier caliper. Five tablets of each formulation were picked randomly and dimensions determined.

Uniformity of Weight

The test was performed according to specifications given in the Indian Pharmacopoeia, 2007 on 20 tablets which was selected randomly. The maximum

acceptable limit is ±7.5% deviation of not more than two of the individual mass from average mass and none deviates by more than twice this percentage.

Measurement of Tablet Friability

Tablet friability was measured using the Roche Friabilator according to I.P. The friability was determined by following formula

$$F = WA\text{-}WB/WA \times 100$$

Where F = Friability; WA = Initial weight (g); WB = Final weight (g).

Limit of friability for tablets under 1% is acceptable.

Measurement of Tablet hardness

The crushing strength of tablets was measured by a Monsanto Hardness Tester.

Wetting Time

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

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

$$R = (WA\text{-}WB) / WB \times 100$$

Where, WB= Weight of tablet before water absorption; WA= Weight of tablet after water absorption

In vitro disintegration time

The process of breakdown of a tablet into smaller particles is called as disintegration. The *in-vitro* disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using distilled water maintained at 37 ± 2°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 7.4 maintained at 37 ± 2°C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

In vitro dissolution studies

Dissolution rate was studied by using IP type-I apparatus (50 rpm) using 900 ml of water as dissolution medium. Temperature of the dissolution medium was maintained at 37.5°C. The bath liquid is kept in constant and smooth motion during the testing. The sample was withdrawn at a regular time interval, filtered and diluted with the medium if necessary. The absorbance of filtered solution was measured by UV spectrophotometric method at 250 nm and concentration of the drug was determined from standard calibration curve.

Drug Content

At random 20 tablets were weighed and powdered. The powder equivalent to 50 mg was weighed accurately and dissolved in 100 ml of phosphate buffer of pH 6.8. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatman No. 1 filter paper. Then the serial dilutions were carried out. The absorbance of the diluted solutions was measured at 250 nm. The concentration of the drug was computed from the standard curve of the Losartan potassium in phosphate buffer of pH 6.8.

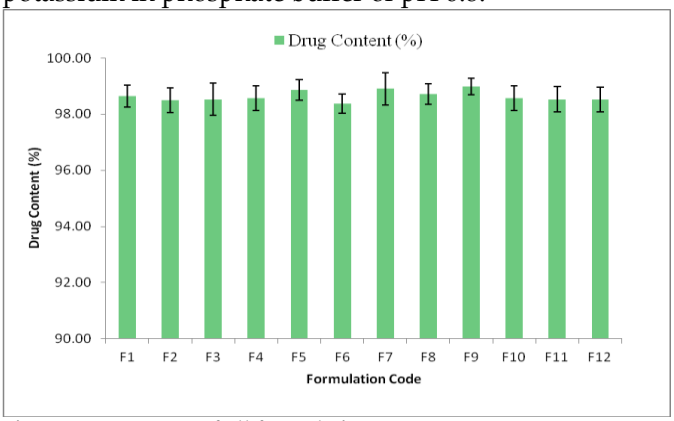

Fig. 1: Drug content of all formulations

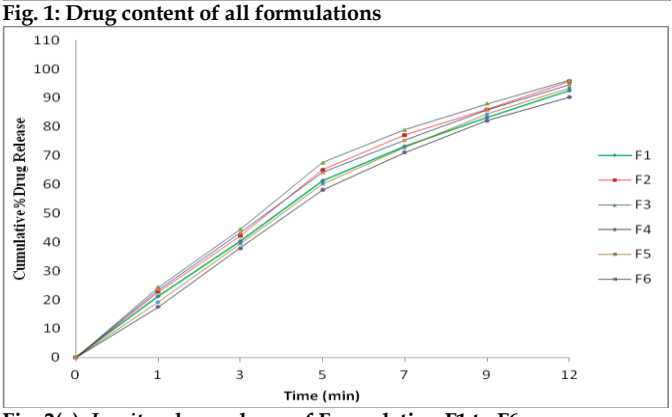

Fig. 2(a): *In vitro* drug release of Formulation F1 to F6

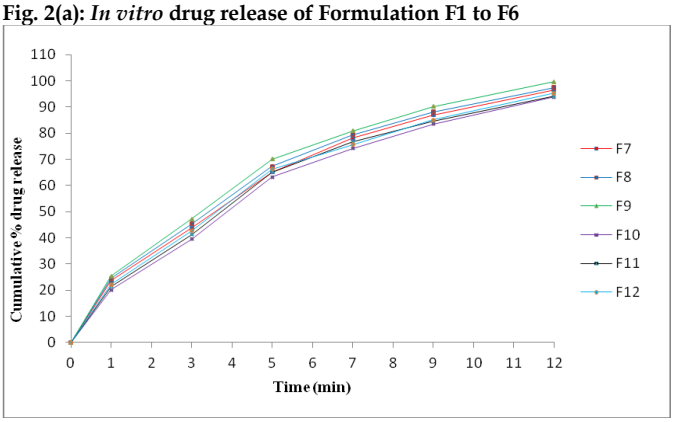

Fig. 2(b): *In vitro* drug release of Formulation F7 to F12

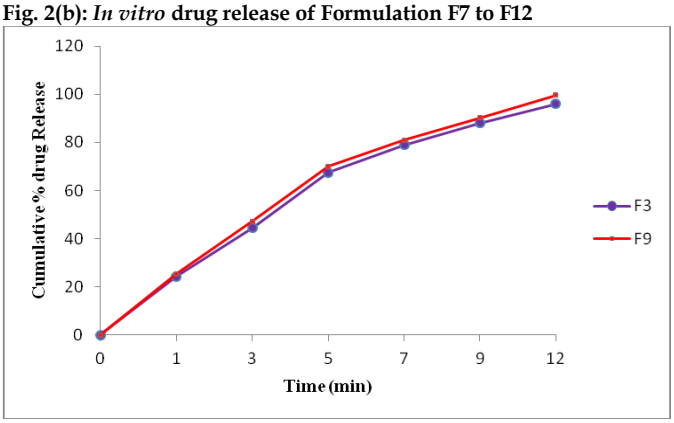

Fig. 2(c): *In vitro* drug release of Formulation F3 and F9

Table 1: Formulations of losartan potassium fast dissolving tablets prepared by direct compression method (1 tablet)

Ingredients (mg)	Formulation Code											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Losartan Potasium	25	25	25	25	25	25	25	25	25	25	25	25
Banana Powder	5	7	10	-	-	-	-	-	-	-	-	-
Apple Pectin	-	-	-	5	7	10	-	-	-	-	-	-
Banana Powder + Crosspovidone	-	-	-	-	-	-	3+2	4+3	5+5	-	-	-
Apple Pectin + Cross Povidone	-	-	-	-	-	-	-	-	-	3+2	4+3	5+5
MCC	78.5	77.5	76	78.5	77.5	76	78.5	77.5	76	78.5	77.5	76
D-Mannitol	78.5	77.5	76	78.5	77.5	76	78.5	77.5	76	78.5	77.5	76
HPMC	7	7	7	7	7	7	7	7	7	7	7	7
SLS	2	2	2	2	2	2	2	2	2	2	2	2
Zinc stearate	2	2	2	2	2	2	2	2	2	2	2	2
Aspartame	1	1	1	1	1	1	1	1	1	1	1	1
Mixed Fruit flavour	1	1	1	1	1	1	1	1	1	1	1	1
Total	200	200	200	200	200	200	200	200	200	200	200	200

Table 2: Evaluation of pre compression parameters

S. No.	Formulation Code	Angle of Repose	Bulk Density	Tap Density	Carr's Index	Hausner's Ratio
1.	F1	28.36 ± 0.44	0.457 ± 0.002	0.530 ± 0.003	13.807 ± 0.104	1.160 ± 0.001
2.	F2	28.06 ± 0.68	0.468 ± 0.002	0.542 ± 0.004	13.642 ± 0.596	1.158 ± 0.007
3.	F3	29.53 ± 0.66	0.479 ± 0.002	0.557 ± 0.004	14.044 ± 0.637	1.163 ± 0.008
4.	F4	33.54 ± 0.60	0.472 ± 0.002	0.552 ± 0.004	14.421 ± 0.641	1.168 ± 0.008
5.	F5	29.24 ± 0.43	0.466 ± 0.002	0.530 ± 0.004	12.058 ± 0.616	1.137 ± 0.007
6.	F6	25.94 ± 0.70	0.474 ± 0.003	0.549 ± 0.004	13.763 ± 0.683	1.159 ± 0.009
7.	F7	28.06 ± 0.25	0.472 ± 0.003	0.544 ± 0.004	13.339 ± 0.638	1.153 ± 0.008
8.	F8	26.10 ± 0.46	0.477 ± 0.002	0.552 ± 0.004	13.515 ± 0.646	1.156 ± 0.008
9.	F9	24.06 ± 0.98	0.489 ± 0.003	0.552 ± 0.004	11.464 ± 0.689	1.129 ± 0.008
10.	F10	25.63 ± 0.46	0.495 ± 0.004	0.560 ± 0.004	11.598 ± 0.723	1.131 ± 0.009
11.	F11	25.79 ± 0.26	0.489 ± 0.003	0.573 ± 0.004	14.758 ± 0.082	1.173 ± 0.001
12.	F12	25.79 ± 0.26	0.483 ± 0.003	0.563 ± 0.008	14.203 ± 0.756	1.165 ± 0.010

Table 3 (a): Evaluation of post compression parameters

Formulation Code	Thickness (in mm)	Diameter (in mm)	Hardness (in kg/cm²)	Friability (in percenage)
F1	2.43 ± 0.057	7.76 ± 0.057	4.33 ± 0.152	0.585 ± 0.013
F2	2.26 ± 0.152	7.76 ± 0.057	3.83 ± 0.057	0.728 ± 0.014
F3	2.23 ± 0.115	7.83 ± 0.057	3.63 ± 0.152	0.590 ± 0.011
F4	2.43 ± 0.115	7.83 ± 0.057	3.83 ± 0.305	0.585 ± 0.011
F5	2.26 ± 0.057	7.86 ± 0.057	3.96 ± 0.208	0.448 ± 0.006
F6	2.33 ± 0.057	7.83 ± 0.115	3.70 ± 0.200	0.583 ± 0.011
F7	2.40 ± 0.173	7.83 ± 0.057	3.50 ± 0.400	0.555 ± 0.007
F8	2.43 ± 0.115	7.83 ± 0.057	4.13 ± 0.208	0.588 ± 0.008
F9	2.53 ± 0.115	7.83 ± 0.057	3.96 ± 0.208	0.440 ± 0.004
F10	2.23 ± 0.115	7.83 ± 0.057	3.70 ± 0.100	0.492 ± 0.008
F11	2.50 ± 0.100	7.76 ± 0.057	4.03 ± 0.230	0.540 ± 0.008
F12	2.36 ± 0.057	7.83 ± 0.057	4.06 ± 0.152	0.689 ± 0.007

Table 3 (b): Evaluation of post compression parameters

Formulation Code	Uniformity of Weight (in mg)	Wetting Time (in sec)	Water Absorption ratio (%)	Disintegration Time (in sec)
F1	198.85 ± 1.926	46	55.08	40.66 ± 1.254
F2	201.15 ± 1.814	41	58.56	39.66 ± 0.577
F3	200.60 ± 1.984	35	56.55	36.66 ± 1.527
F4	201.10 ± 1.832	53	59.56	51.33 ± 1.154
F5	200.60 ± 1.875	53	55.87	51.66 ± 1.527
F6	198.90 ± 1.889	52	60.46	54.66 ± 1.154
F7	198.75 ± 1.970	32	55.16	36.66 ± 1.154
F8	201.45 ± 1.904	35	61.42	28.66 ± 1.154
F9	200.40 ± 1.902	31	58.23	26.33 ± 1.152
F10	198.50 ± 1.986	54	55.23	41.33 ± 1.154
F11	198.85 ± 1.980	44	60.13	37.66 ± 0.570
F12	201.10 ± 1.803	47	59.16	33.66 ± 1.540

RESULTS AND DISCUSSION

Pre formulations studies

The results for characterization of blended powder are shown in Table 2**.** The bulk density of blend varied between 0.574-0.649 g/cm^3. The tapped density was found in the range of 0.746-0.666 g/cm^3. By using these two density data, Hausner's ratio and compressibility index was calculated. The powder blends of all formulation had Hausner's ratio of less than 1.25 indicating good flow characteristics. Blends having value of compressibility index less than 25% were considered as free flowing ones. The values for compressibility index were found between 12.346-13.868.

The flow ability of the powder was also evidenced by the angle of repose. The angle of repose below 35°

ranges indicates good flow properties of powder. The angle of repose was found to be in range 27-34°. 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.

Post Compression studies

Appearance

All the tablets were white in colour, flat in shape with smooth surface without any defects.

Uniformity of thickness

The diameters of all the formulations was almost uniform (7.7-7.8 mm).Thickness of all the formulations was found to be within the range of 2.23 mm to 2.53 mm shown in Table 3(a).

Weight Uniformity

All the tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5%. It is related to tooling of the compression machine, head pressure, machine speed and flow properties of the powder.

Hardness

The hardness of the Mouth dissolving tablet was found in the range of 3.5 to 4.3 kg/cm^2 is given in Table 3 (a).

Friability

Friability was observed less than 1% represented in Table 3(a), indicated that Mouth Dissolving Tablets had a good mechanical resistance. It is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping.

Wetting time

The wetting time was rapid in all the formulations. Wetting is closely related to inner structure of tablets, this may be due to ability of swelling and also capacity of absorption of water. Among all the formulations F9 showed less wetting time. The result was shown in Table 3(b).

Water absorption ratio

The capacity of disintegrant to swell in presence of little amount of water were found to be in the range of 54-66 % as shown in Table 3(b). The water absorption ratio that is the up taking of water was very fast and the ratio was found higher.

***In-vitro* Disintegration time**

Apple pectin & Banana Powder when comes in contact with water they quickly wicks water into the tablet through capillary action to create internal pressure that disintegrates tablet. The disintegration time is shown in Table 3 (b).

Drug Content

The drug content was found to be within the range of 98.38 to 98.99 indicating uniform distribution of drug in the formulated tablets as per pharmacopoeia specification. The Drug content of all formulations was given in Figure 1.

***In vitro* drug release studies**

The comparative drug release was shown in Figure 2(a), 2(b) and 2(c). Formulations F1 containing superdisintegrant Banana (2.5%), F2 containing superdisintegrant Banana (3.5%), F3 containing superdisintegrant Banana (5%), F4 containing superdisintegrant apple pectin (2.5)%), F5 containing superdisintegrant apple pectin (5%), F6 containing superdisintegrant apple pectin (5%), F7 containing superdisintegrant banana powder (1.5%) & cross povidone (1%), F8 containing superdisintegrant banana powder (2%) & cross povidone (1.5%), F9 containing superdisintegrant banana powder (2.5%) & cross povidone (2.5%), F10 containing superdisintegrant apple pectin (1.5%) & cross povidone (1%), F11 V containing superdisintegrant apple pectin (2%) & cross povidone (1.5%) and F12 containing superdisintegrant apple pectin (2.5%) & cross povidone (2.5%) showed a release of 92.58%, 95.76%, 96.01%, 93.45%, 94.53%, 96.56%, 97.46%, 99.68%, 93.86%, 94.06% and 95.34% respectively within twelve minutes. Among all the formulations resultant formulation F9 showed best release of 99.68% within twelve minutes.

The result was obtained and the conclusions drawn from the study are as follows:

- Losartan Potassium fast disintegrating tablet was prepared by direct compression method by using banana powder and apple pectin as superdisintegrants. Total 12 formulations were prepared and characterized.
- All the formulations showed fast disintegration of tablet. As the amount of banana powder and pectin increased in the formulation, there was decrease in disintegration of time.
- It was concluded that formulation F9 was the ideal batch from all the formulations which shows less disintegration time and maximum drug release within twelve minutes

ACKNOWLEDGEMENTS

The authors would like to thank School of Pharmacy, Abhilashi University, Mandi, Himachal Pradesh, India for providing research facilities.

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HOW TO CITE THIS ARTICLE: Kumari B, Soni A, Singla S, Goyal S, Thakur S, Mahant S. Formulation & Evaluation of Mouth Dissolving Tablets Containing Losartan Potassium Using Natural Superdisinigrants. Int. J. Pharm. Sci. Drug Res. 2017; 9(5): 234-239. **DOI: 10.25004/IJPSDR.2017.090506**