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Research Article

Formulation and evaluation of mouth dissolving tablets of losartan potassium by direct compression techniques

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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 Polyplasdone XL 10, Croscarmellose sodium and Explotab in different concentration and evaluated for the pre-compression parameters such as bulk density, compressibility, angle of repose etc. The prepared batches of tablets were evaluated for hardness, weight variation, friability, drug content, disintegration time and in-vitro dissolution profile and found satisfactory. Among all, the formulation F3 containing 5%w/w superdisintegrant Polyplasdone XL 10 was considered to be best formulation, which release up to 99.26% in 12 min.

Keywords: Losartan potassium; Mouth dissolving tablet; superdisintegrants; Dissolution rate.

INTRODUCTION

Recent advance in novel drug delivery system aims to enhance the safety and efficacy of the drug molecule by formulating a dosage form being for the administration (Kuchekar BS, 2003). Difficulty in swallowing is experienced by patient such as pediatric, geriatric, bedridden, disabled and mentally ill, including motion sickness and sudden episodes of allergic attacks, hence resulting in higher incidence of non-compliance and ineffective therapy (Seager H, 1998). To improve the quality of life and treatment compliances of such patients fast disintegrating or orally disintegrating tablets dosage form is a better alternative for oral medication (Yutaka M, 2002). Mouth dissolving tablets are solid dosage form containing medical substances which disintegrate rapidly, usually within few seconds when placed upon tongue requiring no additional water to facilate swallowing (Shu T, 2002, Bradoo R, 2001). It is suited for tablets undergoing high first pass metabolism and is improving bioavailability with reducing dosing frequency to minimize side effect.

Losartan potassium is an angiotensin II receptor antagonist (Gokel Y, 1999). It suppresses the effects of angiotensin II at its receptors, thereby blocking the renninangiotensin system. The rennin-angiotensin system plays a crucial role in the control of blood pressure, and in particular it is felt to play crucial role in hypertension. Losartan has been demonstrated to be superior to previous peptide receptor antagonists and angiotensin converting enzyme (ACE) inhibitors because of its enhanced specificity, selectively, and tolerability (Dias CL, 2005). Generally, losartan potassium is employed in the management of essential hypertension with lower incidence of side-effects like cough (Sivakumar T, 2007). It is readily absorbed and undergoes rapid hepatic metabolism to an active metabolite, EXP-3174, via cytochrome P-450 system.

Various techniques can be used to formulate fast dissolving tablets. Direct compression one of the techniques requires the incorporation of a superdisintegrants into the formulation the use or highly water soluble excipients to achieve fast tablet disintegration (Indurwade NH, 2002). Direct compression dose not require the use of water or heat during the formulation procedure and is the ideal method for moisture and heat-labile medications.

The aim of purpose work was to formulate and characterization mouth dissolving tablets of losartan potassium for rapid dissolution of drug and absorption, which may produce the rapid onset of action in the treatment of hypertension.

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MATERIALS AND METHODS

Materials

Losartan potassium was obtained as a gift sample from Sai Ram Organics Pvt. Ltd. Hydrabad (India). Polyplasdone XL 10, Explotab and Croscarmellose sodium were gift sample from Signet Chemical Corporation, Mumbai. Microcrystalline cellulose and Mannitol were gift samples from Sunrise Remedies, Ahmedabad, India. All chemicals and reagents used were of analytical grade.

Methods

Preparation of mouth dissolving tablets

Losartan potassium mouth dissolving tablets were prepared by direct compression method. Different concentration of excipients was used to prepare mouth dissolving tablets. Compositions of various formulations are shown in Table 1. All the ingredients of the mouth dissolving tablets of Losartan potassium were weighed and mixed in mortar with the help of pestle, then finally Aspartame and 1mg Magnesium Sterate was added material was slightly compressed on the 8mm flat-faced punch using a Rimek tablet press machine. The total weight of the formulation was maintained 200mg.

Table 1: Formulation of losartan potassium mouth dissolving tablets

Ingredients	FORMULATION CODE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Losartan potassium	50	50	50	50	50	50	50	50	50
Microcrystalline cellulose	80	78	76	80	78	76	80	78	76
Mannitol	55	55	55	55	55	55	55	55	55
Polyplasdone XL 10	6	8	10						
Crosscarmellose sodium				6	8	10			
Explotab							6	8	10
Magnesium Sterate	1	1	1	1	1	1	1	1	1
Aspartame	8	8	8	8	8	8	8	8	8

Pre compression parameters

Angle of repose

Angle of repose was determined using fixed funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose was calculated using formula (Rockville MD, 2007).

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

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

Bulk Density

Apparent bulk density (ρb) was determined by pouring blend into a graduated cylinder. The bulk volume (Vb) and weight of powder (M) was determined. The bulk density was calculated using the formula (Rockville MD, 2007, Liberman HA, 2005).

$$\rho b = M/Vb$$

Tapped Density

The measuring cylinder containing known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and weight (M) of the blend as measured. The tapped density (ρt) was calculated using the formula (Rockville MD, 2007, Mukesh P, 2009).

$$\rho t = M/Vt$$

Carr's compressibility index

The simplex way of measurement of the free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index of the granules was determined by Carr's compressibility index (I) which is calculated by using the following formula (Rockville MD, 2007).

$$I = \{(Vo - Vt)/ Vo\} X 100$$

Hausner ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula (Rockville MD, 2007).

$$\text{Hausner ratio} = \rho t/\rho b$$

Where ρt is tapped density and ρb is bulk density. Lower hausner ratio (< 1.25) indicate better flow properties than higher ones (>1.25).

Post compression parameters

All the batches of tablets were evaluated for various parameters like weight variation, friability, hardness, drug content, disintegration and dissolution and results reported in Table 2.

Weight variation test

Twenty tablets were taken and their weight was determined individually and collectively on a digital weighting balance. The average weight of one tablet was determined from the collective weight (Rockville MD, 2007).

Hardness test

The hardness of the tablet was determined using Monsanto Hardness Tester (Rockville MD, 2007).

Friability test

Six tablets from each batch were examined for friability using Roche Fribilator (Tropical Equipment Pvt. Ltd. Mumbai, India) and the equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated (Rockville MD, 2007).

%Friability = (Loss in weight/Initial weight) x 100

Water absorption ratio

A piece of tissue paper folded twice was kept in a Petri dish (internal diameter 5.5cm) containing 6ml of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The wetted tablet was removed and reweighted. Water absorption ratio, R was determined according to the following equation (Bandari S, 2008).

$$R = 100 (Wa – Wb)/Wb$$

Where Wb and Wb are the weight before and after water absorption, respectively.

Wetting time

A piece of tissue paper folded twice was kept in a Petri dish (inter diameter 5.5cm) containing 6ml of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The time required for complete wetting of the tablet was then recorded (Mukesh P, 2009, Bandari S, 2008).

Content uniformity test

Five tablets were weighed and powdered, 10 mg of equivalent of losartan potassium was weighed and dissolved in suitable quantity of methanol, the solution was filtered suitably diluted and the drug content was analyzed using UV spectrometer at 234 nm.

In vitro disintegration time

The disintegration test was performed using an USP disintegration apparatus, with distilled water at 24 ± 0.5^0C. The time reported to obtain complete disintegration of six tablets were recorded and average was reported (Jha SK, 2008).

In vitro dissolution testing

Dissolution study was conducted for all the formulation using USP type-II apparatus (Electolab, Mumbai, India.). The dissolution test was performed using 900 ml of phosphate buffer (PH 6.8) was taken as the dissolution medium at 50 rpm and $37^0C\pm0.5^0C$. Five milliliters of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 234 nm.

RESULTS AND DISCUSSION

Losartan potassium mouth dissolving tablets of were prepared by direct compression method was carried out by using superdisintegrants like Polyplasdone XL 10, Crosscarmellose sodium and Explotab in 3%, 4% and 5% concentration.

Evaluation of powder blends

The formulated powder blend evaluated and results are shown in table 2. The angle of repose was in the range of 26.63-30.17 indicating the good flow properties. Bulk density was found in the range of 0.55-0.60g/cm^3 and the tapped density between 0.67-0.73g/cm^3. The powder blends of all the formulations had Hausner's factor values which were in the range of 1.152-1.218 indicating good flowability. The compressibility index was found between 13.235-17.910. Hence the prepared blends possessed good flow properties and these can be used for tablet manufacture.

Evaluation of Tablets

All batches of prepared tablets were evaluated for the different parameters and results are shown in table 3. Weight variation for prepared tablets was found within specifications of Indian Pharmacopoeia. Hardness and friability of all formulations were within acceptable limits. Hardness of tablets prepared by direct compression was 3.31±0.34 to 3.93±0.12 kg/cm^2. The friability of all formulations was found to be less than 1.0 % and hence the tablets with lower friability may not break during handling on machines and or shipping. The drug content in different formulation was highly uniform and in the range of 97.89-99.24%. Disintegration time is very important for mouth dissolving tablets which is desired to be less than 60 seconds for orally disintegrating tablets. This rapid disintegration assists swallowing and also plays a role in drug absorption in buccal cavity, thus promoting bioavailability.

All formulations showed disintegration time less than 60 seconds. Among the three superdisintegrants used, Polyplasdone XL 10 showed less disintegrating time followed by crosscarmellose sodium and Explotab. The probable reason may be high gelling tendency of crosscarmellose sodium and Explotab than Polyplasdone XL 10 which causes swelling of tablet mass with subsequent retardation of disintegration. Besides the type, the concentration of superdisintegrant used also affected the disintegration time. In case of the tablets containing Polyplasdone XL 10 and crosscarmellose sodium, an increase in concentration of superdisintegrant resulted in definite decrease in disintegration

Table 2: Evaluation of mixed blend of drug and excipients

Formulation code	Angle of re-pose (θ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's ratio	Compressibility index (%)
F1	29.13	0.57	0.68	1.192	16.176
F2	27.32	0.58	0.69	1.189	15.942
F3	29.52	0.56	0.68	1.214	17.647
F4	28.11	0.59	0.68	1.152	13.235
F5	30.01	0.60	0.73	1.216	17.808
F6	29.26	0.60	0.71	1.183	15.492
F7	30.17	0.59	0.69	1.169	14.492
F8	26.63	0.56	0.67	1.196	16.417
F9	29.22	0.55	0.67	1.218	17.910

Table 3: Evaluation data of the prepared losartan potassium mouth dissolving tablets

Formulation code	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Disintegration time (sec.)	Water absorption ratio	Wetting time (sec.)	% Drug release
F1	3.69±0.02	0.41±0.03	98.23	23±0.31	61.42±0.34	23.21±1.34	92.56
F2	3.93±0.12	0.36±0.07	97.89	19±0.46	60.71±0.35	19.41±1.13	97.45
F3	3.71±0.31	0.29±0.06	99.21	14±0.76	59.26±0.21	17.21±0.21	99.26
F4	3.51±0.25	0.61±0.02	98.34	31±0.53	57.64±0.51	24.62±0.37	90.34
F5	3.36±0.13	0.42±0.06	98.45	25±0.72	58.26±0.29	24.31±1.31	93.21
F6	3.59±0.23	0.51±0.04	99.24	22±0.51	60.41±0.37	22.12±1.11	97.33
F7	3.72±0.37	0.34±0.04	97.92	39±0.43	63.39±0.26	29.32±1.25	88.69
F8	3.42±0.22	0.39±0.02	99.11	26±0.27	65.26±0.44	27.13±1.23	93.23
F9	3.31±0.34	0.41±0.06	98.31	28±0.34	66.04±0.13	24.27±0.73	91.29

time. The same result was found for tablets containing Explotab up to 4%. At 5% concentration, it resulted in slight increase in disintegration time from 26 sec. to 28 sec. This delay in disintegration time might have occurred due to probable blockade of capillary pores in tablet mass as result of formation of viscous plug by Explotab, which subsequently, prevented free access of fluid into tablets.

Wetting time is used as an indicator from the ease of the tablet disintegration in buccal cavity. It was observed that wetting time of tablets was in the range of 17 to 29 seconds. It was observed that type of the disintegrant affected the wetting of the tablets. On comparing superdisintegrants the formulation containing Explotab take more wetting time than crosscarmellose sodium and Polyplasdone XL 10. Wetting is related to the inner structure of the tablets and hydrophobicity of the components. This may be due to the fact that Explotab is disintegrated by swelling mechanism leading to longer wetting time. Water absorption ratio ranged from 57.64-65.26. Polyplasdone XL 10 and crosscarmellose sodium perform their disintegrating action by wicking through capillary action and fibrous structure, respectively with minimum gelling[14]. The relative ability of the various disintegrants to wick water into the tablets was studied. After contact with water the tablets containing Explotab swelled, the outer edge appeared gel-like. Tablets containing Polyplasdone XL 10 quickly wicks water and were hydrated, but were soft as compared with tablets prepared with crosscarmellose sodium and Explotab. The centers of the tablets with Explotab and crosscarmellose sodium remained dry and hard.

In vitro dissolution studies of the prepared mouth dissolving tablets was preformed in pH 6.8 using USP dissolution apparatus type 2. The dissolution rate was found to increase linearly with increasing concentration of superdisintegrant. This was marked by decreased disintegration time values for tablet formulation containing higher proportions of superdisintegrants except for tablet containing 5% Explotab. Formulations F1, F2 and F3 which contained increasing concentrations of Polyplasdone XL 10 from 3%w/w to 5%w/w, have recorded drug release 92.56%, 97.45% and 99.26% respectively, at the end of 12 minutes (Figure 1). Formulations F4, F5 and F6 which contained increasing concentrations of crosscarmellose sodium from 3%w/w to 5%w/w, have recorded drug release 90.34%, 93.21% and 97.33% respectively, at the end of 12 minutes (Figure 2). Formulations F7, F8 and F9 which contained increasing concentrations of Explotab from 3%w/w to 5%w/w, have recorded drug release 88.69%, 93.23% and 91.29% respectively, at the end of 12 minutes (Figure 3). In all the formulations the drug release was near to 100% within 12 minutes. But % drug release value indicated that with the increase in concentration of Explotab from 3%w/w to 4%w/w, the rate of dissolution of tablets was slightly enhanced. However further increase in concentration to 5%w/w did not improve the dissolution rate but infact retarded

it. This was probably due to formation of viscous plugs by Explotab particles. The relative efficiency of different superdisintegrants to improve the dissolution rate of tablets was in order, Polyplasdone XL 10 > Crosscarmellose sodium > Explotab. In comparative study of the formulations F3, F6 and F9 showed 99.26%, 97.33% and 91.29% drug release respectively at the end of 12 minutes, (Figure 4).

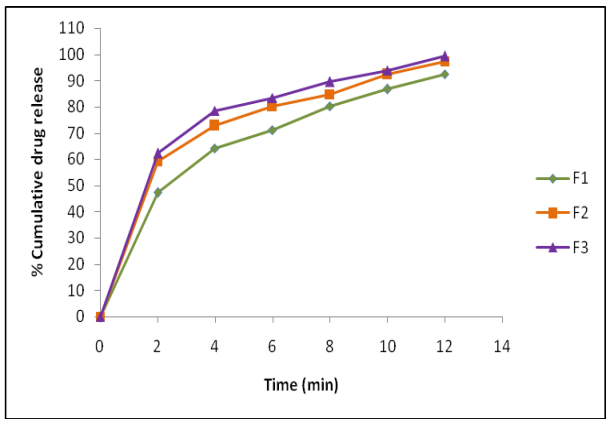

Figure 1: In-Vitro release Profile of formulation F1, F2 and F3

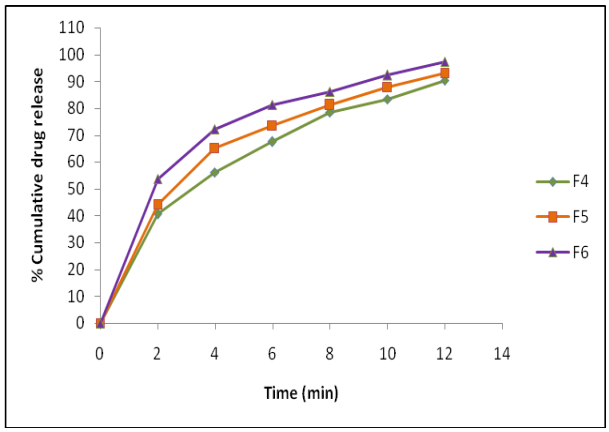

Figure 2: In-Vitro release Profile of formulation F4, F5 and F6

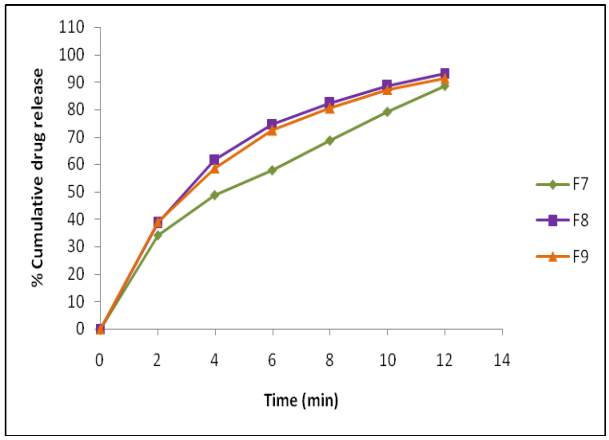

Figure 3: In-Vitro release Profile of formulation F7, F8 and F9

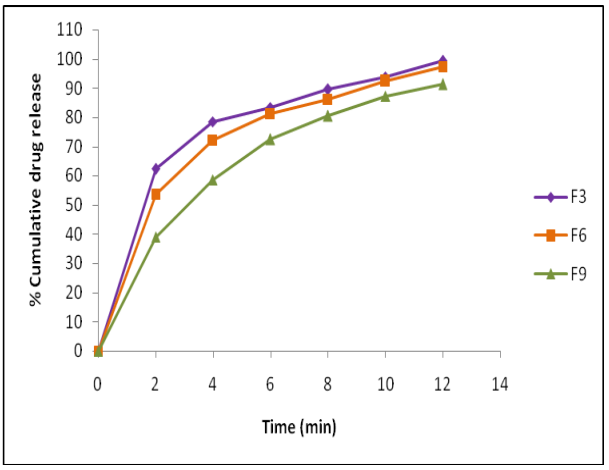

Figure 4: In-Vitro release Profile of formulation F3, F6 and F9

CONCLUSION

It was concluded that mouth dissolving tablets of Losartan potassium can be successfully prepared by direct compression techniques using selected superdisintegrants for the better patients compliance and effective therapy. The relative efficiency of these superdisintegrants to improve the disintegration and dissolution rate of tablets was in the order, Polyplasdone XL 10 > Crosscarmellose sodium > Explotab.

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