Research Article

Development and Evaluation of Fast Dissolving Oral Film of Losartan Potassium

MD Khaja Azharuddin[1], Mohammed Asadullah Jahangir[1], MD Mazher Ahmed[1], Imran Kazmi[2], Abdul Muheem[3], P. Durga Bhavani[4], MA Saleem[*1]

[1]Department of Pharmaceutics, Luqman College of Pharmacy, Gulbarga, Karnataka, India.
[2]Assistant Professor, Department of Pharmacognosy, Glocal University, Saharanpur, India.
[3]Department of Pharmaceutics, Jamia Hamdard, New Delhi, India.
[4]Assistant Professor, Department of Pharmaceutics, SSJ College of Pharmacy, Hyderabad, India.
[*1]Head of Department, Department of Pharmaceutics, Luqman College of Pharmacy, Gulbarga, Karnataka, India.
***Corresponding author's E-mail:** ssaleempharm@gmail.com

Accepted on: 22-09-2015; **Finalized on:** 31-10-2015.

ABSTRACT

Fast dissolving oral film of Losartan potassium were prepared and evaluated with an objective to rapid dissolution of drug and absorption which may produce the rapid onset of action in the treatment of hypertension and provides the convenient means of administration to those patient suffering from difficulty in swallowing such as paediatrics, geriatric, and uncooperative mentally ill patients and also improve the bioavailability of the drug. The fast dissolving oral film were prepared using different polymers like polyvinyl alcohol, polyvinyl pyrollidone, hydroxyl propyl methyl cellulose, carbopol, pectin and tragacanth by solvent casting method. The fast dissolving oral film evaluated for folding endurance, swelling index, surface pH, *in vitro* disintegration time, drug content, drug polymer compatibility (IR Study), and *in vitro* drug release. The physical appearance and folding endurance properties were found to be good and electron microscopy shows that films are clear, colourless with smooth surface without any scratches .The average folding endurance time within the range of 112 to 208. The drug content showed uniform mixing of drug in all prepared fast dissolving films. The *in vitro* drug release showed 78 to 96 % drug release within 5 minutes. Drug release obeys the first order kinetics. The prepared films were stable. Hence it can be inferred that the fast dissolving oral film of Losartan potassium may produce the rapid action thereby improving bioavailability and enhance the absorption by avoiding the first pass effect.

Keywords: Losartan potassium, Polyvinyl alcohol, Polyvinyl pyrollidone, Hydroxyl propyl methyl cellulose, Carbopol, Fast dissolving oral films.

INTRODUCTION

Recent developments in technology have presented viable dosage alternatives for patients who may have difficulty in swallowing of tablets or liquids. Conventionally oral solid dosage form are administered with a glass of water may be inconvenient or impractical for some patients.[1] The oral cavity has been investigated as a site for drug delivery from a long period of time about 60% of the total dosage forms are administered by oral route.[2] Among the different routes of administration, the oral route of administration continues to be most preferred route due to various advantages including ease of administration, avoidance of pain, versatility and most importantly patient compliance. One such relatively new dosage form is the oral strip, a thin film that is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity. Recently, fast dissolving drug delivery system have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better compliance. These delivery systems either dissolve or disintegrate in mouth rapidly, without requiring any water to aid in swallowing.[3] They also impart unique product differentiation, thus enabling use as line extensions for existing commercial products. This novel drug delivery system can also be beneficial for meeting the current needs of the industry for improved solubility/stability, biological half life and bioavailability enhancement of drugs.[4]

Many pharmaceutical dosage forms are administered in the form of pills, granules, powders and liquids. Generally, a pill is designed for swallowing intact or chewing to deliver a precise dosage of medication to patients. The pills, which include tablet and capsules, are able to retain their shapes under moderate pressure. However, some patient, particularly paediatric and geriatric patients, have difficulty in swallowing or chewing solid dosage forms.[5,6]

Many paediatric and geriatric patients show unwillingness to take solid preparation due to fear of choking.[7]

Although oral disintegrating tablets have an advantage of administration without choking and fast disintegration; the disintegrated materials contained in them are insoluble and remain same until swallowing. In such cases formulation of fast dissolving film will be advantageous.[8,9]

Hence orally dissolving tablets have come into existence. Even with these differences, most of the existing oral dissolving drug delivery systems are in the form of solid tablets and designed to dissolve/disintegrate in the patient's mouth without the need to drink or chew. However, the fear of taking solid tablets and the risk of choking for certain patient populations still exist despite their short disintegration/dissolution times. Hence mouth

dissolving oral film drug delivery is a better alternative in such cases. Many drugs given orally are poor in bioavailability because of the pH of the stomach, the presence of enzymes, and extensive first-pass metabolism. Traditionally, these drugs have been administered by parenteral route, which invariably lead to poor patient compliance.

Losartan Potassium, an anti-hypertensive, is an angiotensin II type AT1 receptor antagonists which interfere with the binding of angiotensin II to the angiotensin II AT1-receptor by, themselves, binding reversibly to the receptors in vascular smooth muscle and the adrenal gland. As angiotensin II is a vasoconstrictor, which also stimulates the synthesis and release of aldosterone, blockage of its effects results in decrease in systemic vascular resistance.[10]

MATERIALS AND METHODS

Materials

Losartan Potassium was obtained as a gift sample from Micro Labs, Bangalore. HPMC, Polyvinyl alcohol, polyvinyl pyrollidone, croscarmellose sodium and sodium starch glycolate were purchased from SD Fine Chemicals Ltd., Mumbai. All the other ingredients used were of analytical grade.

Preparation of fast dissolving oral film of Losartan potassium

Oral fast dissolving film was prepared by solvent casting method. Aqueous solution I was prepared by dissolving film forming polymer, in specific proportion in distilled water and allowed to stirred for 3 hours and kept for 1 hour to remove all the air bubble entrapped or remove bubbles. Aqueous solution II was prepared by dissolving the pure drug, sweetener, and plasticizer in specific proportion in distilled water. The aqueous solution I and II were mixed and stirred for 1 hour. The solutions were cast on to 9cm diameter Petri dish and were dried in the oven at 45^{o}C for 12 hours.[11]

The film was carefully removed from surface of Petridish and cut according to size required for testing (square film 1.5 cm length, 1.5cm width). The samples were stored in glass container maintained at a temperature 30^{o}C and relative humidity 60% ± 5% until further analysis. The formulation amount of all the ingredients is tabulated in table 1, table 2 and table 3.

Formulation of fast dissolving film of Losartan potassium

Calculation of dose for Losartan Potassium: The dose of Losartan Potassium is 25mg. Therefore, amount of Losartan Potassium required in 3cm (1.5x1.5) film is 25mg.

i) Area of film of 1.5X1.5 sq.cm is 2.25 sq.cm.

ii) Area of petridish of 6cm diameter is 28.26 sq.cm.

iii) Amount of drug present in 2.25 sq.cm of film is 25 mg.

iv) Amount of drug present in 28.26 sq.cm of Petridish is 314 mg.

Therefore, 2.25 sq.cm of film should contain 25 mg of drug. It is fixed for all formulations.

Characterization of fast dissolving oral films by IR Spectroscopy

The samples of the fast dissolving films were prepared in the form of KBr pellets and subjected for the scanning in the range of 4000 cm^{-1} to 400 cm^{-1} using FTIR spectrophotometer.[12]

Evaluation of fast dissolving oral films

Losartan potassium films were evaluated for the following properties-

Physical appearance and surface texture of the film

This parameter was evaluated by doing visual inspection of films and texture of films.

Thickness of film

Thickness of the prepared films was measured using screw gauge with a least count of 0.01 mm at different spots of the film.[13] Averages of the measurement at three different spots were calculated.

Folding endurance

Folding endurance is determined by repeated folding of the whole film at a particular place till the film breaks.[4] Folding endurance value is computed by the number of times the film resists from breaking up.

Moisture uptake

The moisture uptake by the films are determined by exposing the films to an environment of 40^{o}C with 75% relative humidity for 1 week.[13] The uptake of moisture by the films was calculated as the measure of the percent increase in weight.

Uniformity of drug content

This parameter was determine by dissolving one film of dimension 1.5x1.5 cm containing 25 mg of Losartan potassium by homogenization in 100 ml of pH 6.8 phosphate buffer for 30 minutes with continues shaking. From this, 10ml was withdrawn and diluted to 50ml using PH 6.8 buffer solution.[12] The absorbance was measured at 203nm using an UV spectrometer.

Swelling index

The swelling index of the oral film was studied using pH 6.8 phosphate buffer solutions. The film sample (surface area 3cm) was weighed and placed in a pre-weighed stainless steel wire sieve of approximately 800-µm mesh. The film was placed in the mesh and was submerged into 50 ml of pH 6.8 phosphate buffer solution.

The stainless steel mesh was removed at fixed time intervals; excess of the moisture was carefully wiped out with absorbent tissue and reweighed. Increase in weight

of the film was determined at each time interval until a constant weight was observed.[12]

The degree of swelling was calculated using the formula:

SI = Wt- Wo **/** Wo

Where SI is the swelling index, Wt is the weight of the film at time —t and Wo is the weight of film at t=0.

Surface pH of films

The surface pH was evaluated by using digital pH meter. The prepared oral film was slightly wet using water. The pH was measured by bringing the combined glass electrode in contact with surface of the films.[4]

***In-vitro* disintegration study**

Electrolab Disintegration Tester ED-2L (USP) was employed for the *in-vitro* disintegration study of the fast dissolving oral. One piece of the prepared film was placed in each of the six tubes of the basket. The disc was added to each tube and the apparatus was run using 900 ml of pH 6.8 phosphate buffer solutions as the immersion liquid. The assembly was raised and lowered between 30 cycles per minute in distilled water maintained at 37±0.5^{o}C.[4] The time in seconds was measured and recorded for complete disintegration of the oral film with no palatable mass remaining in the apparatus.

***In-vitro* dissolution study**

Electrolab Tablet Dissolution Tester USPXXIII (basket type) was employed for the study of *in-vitro* release of fast dissolving oral film of Losartan potassium. Drug loaded film equivalent to 25 mg of drug was introduced into 900ml of the dissolution medium pH 6.8 phosphate buffer which was maintained at 37±0.5 ^{o}C with basket rotating at a speed of 50 rpm. Aliquots are withdrawn at fixed intervals and analyzed spectrophotometrically using shimadzu-1700 UV-Visible spectrophotometer.[4] The dissolution studies were carried out in triplicate in pH 6.8 phosphate buffer for 5 minutes. At every sampling time the volume of dissolution medium was adjusted to 900ml by replacing 5ml with same dissolution medium.

***In-vitro* drug release studies details**

USP XXIII dissolution test apparatus was employed to study the *in-vitro* drug release using pH 6.8 phosphate buffer solutions, volume 900 ml maintained at the temperature of 37±0.5^{o}C as the dissolution medium. The basket speed was fixed at the speed of 50 rpm. After every 30 sec and 1 min sampling was done throughout the procedure. Each time 5 ml of the sample was withdrawn.[12] The absorbance was measured at 203 nm.

Stability studies

The aim of stability testing is to provide prominent evidence on how the quality of drug substance or drug product may varies with time under the influence of a variety of environmental factors like temperature, humidity and light and to establish retest period for the drug substance or a shelf life for the drug product and recommended storage condition.

From among the different formulations the stability studies were carried out on some selected ones by storing them in amber coloured bottle tightly plugged with cotton and capped at 40±0.5^{o}C and 75.0± 5% RH for 3 month.[13] The formulations were evaluated for physical appearance, drug content and *in vitro* dispersion time at 1month interval time.

RESULTS AND DISCUSSION

It was clear from the FTIR spectrophotometric observations that the characteristics absorption bands for different functional groups and bonds of the drug and its polymer that is most of the cases there is no appreciable change in the position of the bands. Even if negligible deviation exists, it's due to the different types of the polymers used for the study. Hence it is clear that the drug has not undergone any type of structural change or any chemical reaction with the polymers and other excipients used. Therefore it can be concluded that in the present investigation there is no interaction of the drug with the polymers and the excipients used. The FTIR spectra of Losartan potassium is shown in figure1.

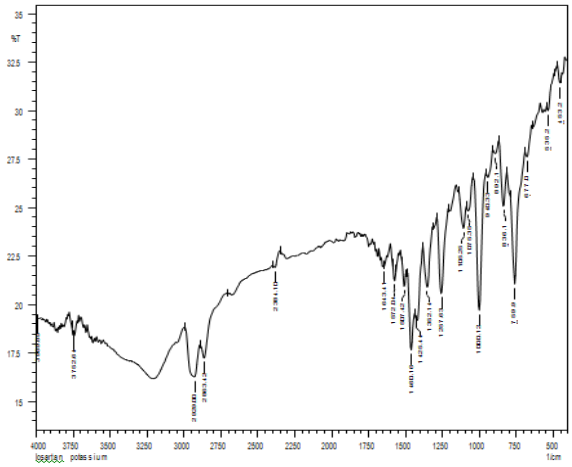

Figure 1: FTIR spectra of Losartan potassium

The weight of the prepared films was determined using digital balance and the average weight of the all the films was given in table 4. All the films are within the weight range of 43.10 ± 0.110 to 60.29 ± 1.210 mg indicates that all the films are in uniform weight with minimum standard deviation.

All the films are free from the moisture uptake and there is no evidence of moisture attack in the prepared films.

The thickness of the film was measured using screw gauge micrometer. The thickness was almost uniform in all the formulations and values ranges from 0.7 ± 0.057 mm to 1.1 ± 0.100 mm. The standard deviation values indicated that all the formulations were within the range.

Among all the formulations, Formulation F1 to F3 showed minimum folding endurance time which indicates that these fast dissolving films are excellent in flexibility as

compared to other formulations. The folding endurance data of all the films is given in table 4.

The drug content uniformity was performed for all the 15 formulations and results are shown in table 5. The percentage drugs content of the fast dissolving films were found to be between 88.33% ± 0.027 to 98.68% ± 0.034 of Losartan potassium. The results were within the range and that indicated uniformity of mixing and is given in table 4.

The *in vitro* disintegration time is calculated by the time taken by film to undergo complete disintegration. The disintegration time of different formulation are tabulated in table 4.

The *in-vitro* disintegration time of all the formulations falls within the range of 16 ± 1.528 to 49 ± 2.887 seconds fulfilling the official requirements. As the concentration of the super-disintegrants increases the *in-vitro* disintegration time of the film decreases.

The study for swelling index is carried out in pH 6.8 phosphate buffer solution and the readings are tabulated in table 4. The formulation F14 and F15 showed higher swelling index as compared to the other formulations due to the more water absorption of the super-disintegrants.

The *in vitro* drug release study of fast dissolving film from each batch F1 to F15 was carried out. The plot of % cumulative drug release v/s time plotted and depicted as shown in figure 2 to figure 3. From the *in vitro* dissolution data, it was found that, the drug release study of the fast dissolving film (F1to F4) formulation were about 89.11%, 82.43%, 79.60%, and 78.40% drug release respectively. The *in vitro* drug release of fast dissolving film (F5 to F8) formulation were about 89.11%, 82.43%, 79.60% and 78.40% drug release respectively. The *in vitro* drug release of fast dissolving film (F9 to F12) formulations were showed 75.54%, 78.99%, 90.22% and 80.14% drug release respectively. The *in vitro* drug release of fast dissolving film (F13 to F15) formulation were about 81.73%, 93.14%, and 96.83% drug release respectively. It was observed from the result that, formulation F14 & F15 shows maximum drug release in 2%PVA with 0.5% PVP with 25% sodium starch glycolate is 93.14% and 2% HPMC with 0.5% with 30% croscarmellose sodium is 96.83% drug release.

Table 1: Formulation table of Losartan Potassium oral films

Formulation Code	Losartan Potassium (gm)	PVA %W/V	PVP %W/V	HPMC %W/V	Pectin %W/V	Aspartame %W/W of polymer	Propylene Glycol %W/W of polymer
F1	3.14	2.0	0.5	-	-	7.0	30.0
F2	3.14	1.0	-	1.5	-	7.0	30.0
F3	3.14	-	0.5	2.0	-	7.0	30.0
F4	3.14	-	0.5	-	2.0	7.0	30.0
F5	3.14	1.0	-	-	1.5	7.0	30.0

Table 2: Formulation table of Losartan Potassium oral films

Formulation Code	Losartan Potassium (gm)	PVA %W/V	Carbopol %W/V	HPMC %W/V	Tragacanth	Pectin %W/V	Aspartame %W/W of polymer	Propylene Glycol %W/W of polymer
F6	3.14	-	-	1.5	-	1.0	7.0	30.0
F7	3.14	2.0	0.20	-	-	-	7.0	30.0
F8	3.14	-	0.20	2.0	-	-	7.0	30.0
F9	3.14	-	0.20	-	0.20	2.0	7.0	30.0
F10	3.14	-	-	-	-	2.0	7.0	30.0
F11	3.14	1.5	-	1.0	-	-	7.0	30.0
F12	3.14	-	-	2.0	0.20	-	7.0	30.0
F13	3.14	2.0	-	-	0.20	-	7.0	30.0

Table 3: Formulation table of Losartan Potassium oral films

Formulation Code	Losartan Potassium (gm)	PVA %W/V	PVP %W/V	HPMC %W/V	SSG %W/W of polymer	CCS %W/W of polymer	Aspartame %W/W of polymer	Propylene Glycol %W/W of polymer
F14	3.14	1.5	-	1.0	25.0	-	7.0	30.0
F15	3.14	-	0.20	2.0	-	30.0	7.0	30.0

PVA = Polyvinyl alcohol, PVP = Polyvinyl pyrrolidone, HPMC = Hydroxy propyl methyl cellulose, SSG = Sodium starch glycolate. CCS = Croscarmellose sodium

Table 4: Evaluation of fast dissolving oral film of Losartan potassium

Formulation code	Drug Content Uniformity (%) ± SD, n =3	In vitro Disintegration (sec) ± SD, n =3	Swelling index (%) ± SD, n =3	Folding Endurance ± SD, n=3
F1	93.91% ± 0.047	19 ± 3.606	64.65 ± 2.263	112 ± 2.517
F2	92.90 ± 0.056	22 ± 1.00	60.24 ± 2.234	123 ± 3.215
F3	95.94 ± 0.035	22 ± 2.517	58.33 ± 3.608	123 ± 4.726
F4	91.27 ± 0.063	42± 2.887	65.27 ± 2.402	144 ± 3.215
F5	96.65 ± 0.058	31 ± 1.000	62.22 ± 3.845	133 ± 4.509
F6	91.58 ± 0.049	38 ± 2.517	56.60 ± 5.920	149 ± 2.082
F7	90.06 ± 0.027	45 ± 1.051	48.66 ± 3.395	171 ± 3.606
F8	89.55 ± 0.025	49 ± 2.887	2.08 ± 3.608	184 ± 4.041
F9	88.33 ± 0.027	47 ± 2.646	57.77 ± 3.851	197 ± 2.517
F10	91.27 ± 0.043	38 ± 2.517	63.80 ± 3.920	162 ± 3.606
F11	95.63 ± 0.032	19 ± 1.528	65.79 ± 4.440	133 ± 3.055
F12	90.87 ± 0.015	19 ± 1.428	54.16 ± 3.608	208 ± 2.887
F13	88.84 ± 0.015	39 ± 4.00	48.88 ± 3.851	201 ± 3.512
F14	96.85 ± 0.041	17 ± 1.528	69.08 ± 3.608	142 ± 3.055
F15	98.68 ± 0.034	16 ± 1.528	71.16 ± 3.608	141 ± 3.606

Table 5: Regression analysis and correlation coefficient r‟ values of the *in-vitro* release data

Formulations	Zero order		First order	
	„R2‟	SSR	„R2‟	SSR
F1	0.846	2.067	0.931	0.005
F2	0.820	2.048	0.910	0.005
F3	0.850	2.075	0.920	0.005
F4	0.745	2.010	0.916	0.005
F5	0.757	2.017	0.849	0.152
F6	0.864	2.088	0.920	0.147
F7	0.747	2.072	0.907	0.132
F8	0.820	2.090	0.917	0.132
F9	0.722	2.082	0.897	0.124
F10	0.776	2.043	0.906	0.136
F11	0.784	2.045	0.865	0.006
F12	0.820	2.093	0.940	0.004
F13	0.090	2.069	0.950	0.004
F14	0.805	2.093	0.913	0.010
F15	0.763	2.189	0.853	0.016

The release mechanism of fast dissolving oral film of Losartan potassium was also evaluated on the basis of theoretical dissolution equation including zero order, and first order. To obtain a better understanding the residual analysis of the said model was performed. The goodness of fit was evaluated using the regression coefficient r‟ and the sum of squared residuals (SSR) value. The correlation coefficient r‟ and sum of squared residual (SSR) value of kinetic models are summarized in table 5. The curve linear nature of percent drug released versus time plots suggested that none of the formulations follows zero order drug release kinetics, which was confirmed by poor correlation coefficient r‟ and high SSR value in all the cases. When the data was fitted to first order kinetic model, a linear relationship was obtained with high r‟ values and small SSR value, suggesting that the drug release followed first order kinetics.

The selected formulations was evaluated for short term stability studies which was stored at 40°C at 75% RH tested for 3 month and were analyzed periodically for their physical parameters, *in vitro* dispersion time and drug content at 30 days interval.

The residual drug contents of formulations were found to be within the permissible limits and were stable for a period of 3 months.

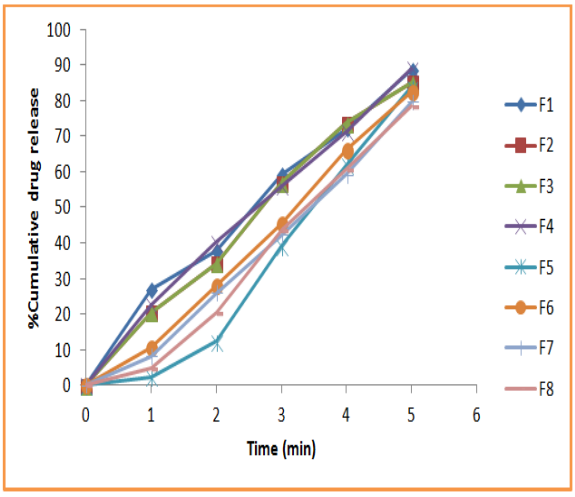

Figure 2: *In-vitro* drug release profile of fast dissolving oral film of Losartan potassium

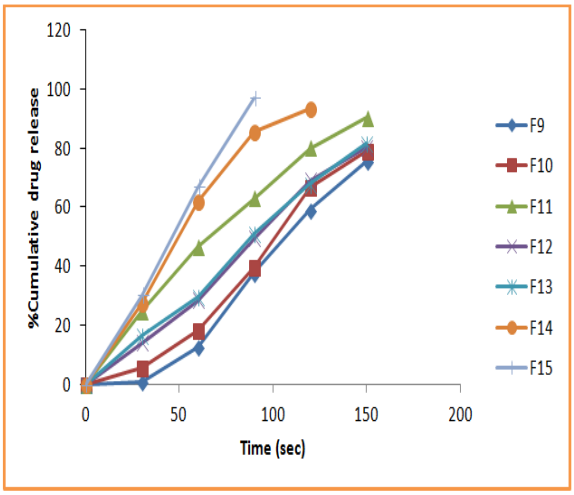

Figure 3: *In-vitro* drug release profile of fast dissolving oral film of Losartan potassium

CONCLUSION

A successful attempt was made to develop oral fast dissolving films of Losartan potassium. From the results it was observed that drug and different polymer combination ratio influence the thickness, folding endurance, drug content as well as the drug release pattern of fast dissolving oral film of Losartan potassium. Hence, the fast dissolving oral film of Losartan potassium are expected to provide clinician with a new choice of safe and more bioavailable formulations in the management of hypertension.

The study reveals satisfactory results with a further scope of pharmacokinetic and pharmacodynamic evaluation.

Acknowledgement: The authors are thankful to the Management, Luqman College of Pharmacy, Gulbarga, Karnataka for providing all the necessary facilities to carry out this research work.

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Source of Support: Nil, **Conflict of Interest:** None.