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Research Article

FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILMS CONTAINING LOSARTAN POTASSIUM

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ABSTRACT

The fast dissolving oral film were prepared using different polymers like PVA, PVP, HPMC, 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 by FTIR Study, Scanning electron microscopy 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 *invitro* 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, PVA, HPMC, fast dissolving film.

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 form 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] . Nearly 35-50 percent of the general population, especially the elderly and children suffer from dysphagia or difficulty in swallowing, which results in high incidence of non-compliance and ineffective therapy. Other group who may experience problems in swallowing conventional oral dosage form are the patients with reduced liquid intake or patients suffering from nausea, as well as patients travelling or who do not have easy access to water. The swallowing problems are also common in some cases such as patients with motion sickness, sudden episodes of allergic attack or coughing and due to no access of water. 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 pediatric and geriatric patients, have difficulty in swallowing or chewing solid dosage formsυ,ϖ. Many pediatric and geriatric patients are unwilling to take these solid preparations due to fear of chokingω. 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 advantageousξ,ψ. 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 or 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 .This made the pharmaceutical industries to look for alternative routes of drug delivery system. Intra oral fast-dissolving drug delivery system where in the dosage form (film) will be placed on the surface of the tongue or in the oral/buccal cavity, where drug release rapidly for local and systemic absorption.

MATERIAL

Losartan potassium is obtained as gift sample from Micro labs, Bangalore., Carbopol934p purchased from Rajesh chemicals, Mumbai., Poly vinyl alcohol, Poly vinyl pyrrolidone k-30, HPMC E-15, Pectin, Traganth gum, Aspartame, Croscarmellose sodium, Propylene glycol Sodium starch glycolate are obtained from SD Fine Chem. Ltd. Mumbai.

METHOD

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 solution were cast on to 9cm diameter Petri dish and were dried in the oven at 45^0C for 12 hours. 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 30^0C and relative humidity 60% ±5% until further analysis.

Formulation of fast dissolving film of losartan potassium

Calculation of dose for losartan potassium

The dose of losartan potassium is 25 mg. Therefore amount of Losartan potassium required in 3cm(1.5x1.5) is 25 mg.

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.

Table 1: Composition of various formulations

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Losartan potassium(gm)	3.14	3.14	3.14	3.14	3.14	3.14	3.14	3.14	3.14	3.14	3.14	3.14	3.14	3.14	3.14
PVA %W/V	2.0	1	-	-	1.0	-	2	-	-	-	1.5	-	2.0	1.5	-
PVP %W/V	0.5	-	0.5	0.5	-	-	-	-	-	-	-	-	-	-	0.20
HPMC %W/V	-	1.5	2.0	-	-	1.5	-	2	-	-	1.0	2.0	-	1.0	2.0
Carbopol %w/v	-	-	-	-	-	-	0.20	0.20	0.20	-	-	-	-	-	-
Pectin %w/v	-	-	-	2.0	1.5	1	-	-	2.0	2.0	-	-	-	-	-
Tragacanth %w/v	-	-	-	-	-	-	-	-	-	0.20	-	0.20	0.20	-	-
Sodium starch glycolate %W/w	-	-	-	-	-	-	-	-	-	-	-	-	-	25.0	-
Croscarmellose sodium %W/w	-	-	-	-	-	-	-	-	-	-	-	-	-	-	30.0
Aspartame %w/v Polymer	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0
Proplyene Glycol %w/w of polymer	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0

RESULT AND DISCUSSION

Standard plot of Losartan potassium in PH 6.8 phosphate buffer

100 mg of losartan potassium was accurately weighed and dissolve into 100 ml volumetric flask containing pH 6.8 buffer solution to get a concentration of (1000 µg/ml) i.e. stock solution-I. from this 1 ml was withdrawn and diluted to 100 ml with pH 6.8 phosphate buffer, to get a concentration of (10 µg/ml) i.e. Stock solution-II.

Calibration curve in ph 6.8 phosphate buffer solution

From the stock solution-II, 1,2,3,4,5,6,7,8and 9ml sample were withdrawn and volume was made up to the mark with pH 6.8 phosphate buffer. This solution gives 1,2,3,4,5,6,7,8,and 9 µg/ml concentration of losartan potassium. The absorbance of these solutions measured in UV at 203 nm using pH 6.8 phosphate buffer as blank.

Table 2: calibration Losartan potassium in 6.8 pH phosphate buffer

Sl. NO	CONCENTRATION(mcg/ml)	ABSORBANCE
1	0.00	0.00
2	01	0.182
3	03	0.300
4	05	0.493
5	07	0.695
6	09	0.903

DRUG AND EXCEPIENT COMPATIBILITY STUDIES

Drug- excipient compatibility studies lay the foundation for designing a chemically stable formulation for clinical and commercial development. Drug excipient compatibility studies are conducted during preformulation to select the most appropriate excipients.

It is clear from the below observation of the below values of 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 exist, its due to the different types of the polymers used for the study.

Table 3: FTIR (KBr) cm-1

Positsons of the bond cm-1	Pure drug	PVA					PVP	CP	PECTIN	HPMC	TRAGACANTH	Remark
3200-3350	3200-3350	-					-	3200-3350	3200-3350	-	-	Brord peak hydrogen bonded –OH of CH2OH
2929-2863	2929-2863	2929-2864					2929-2864	2929-2865	2932-2866	2926-2867	2928-2861	C-H stretching bond,CH2 and CH3 groups.
1643	1643	1643					1643	-	1639	1640	1640	C=N gropup.
1572-1507	1572-1507	1576-1500					1515	1549	1509	1507	1502	C=C ring stretching(aromatic ring)
1460-1352	1460-1461	1461-1352					1462-1370	1454-1352	1457-1356	1459-1359	1461-1355	C-H bending of CH3 and CH2 groups
1425	1425	1426	1430	1411	1424	1424	1424		C-N			
1257	1257	1258	1264	1254	1254	1257	1258		O-H bending			
837-760	837-760	837-760	839-760	839-760	838-757	839-753	839-761		1,4 disubstituted phenyl ring 1,3 disubstituted phenyl ring			

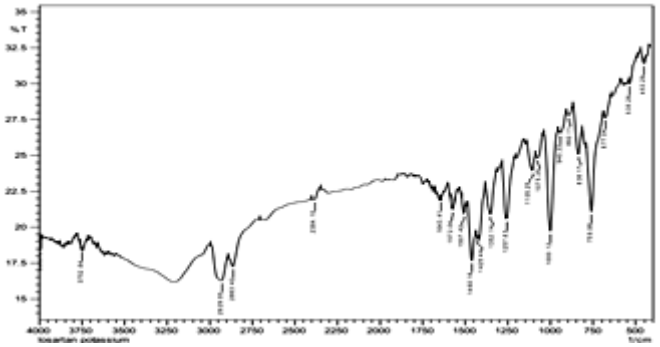

Fig. 2: FTIR OF PURE DRUG (LOSARTAN POTASSIUM)

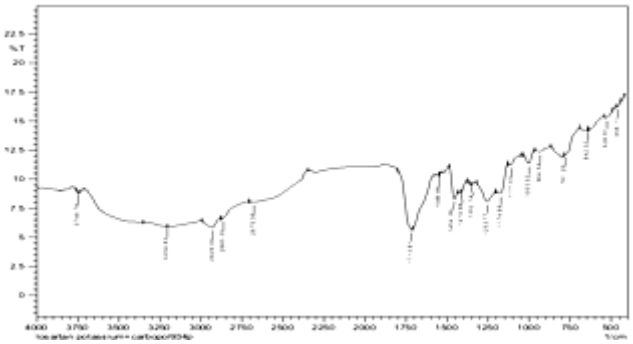

Fig. 3: FTIR OF DRUG + CARBOPOL 934p

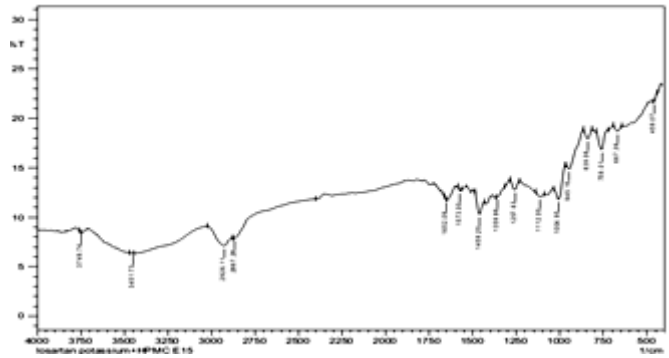

Fig. 4: FTIR OF DRUG + HPMC E-15

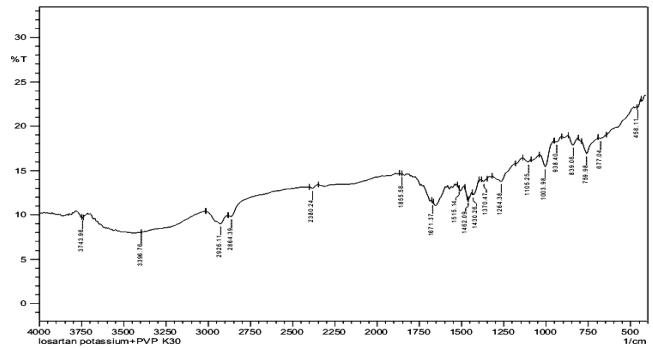

Fig. 5: FTIR OF DRUG + PVP K-30

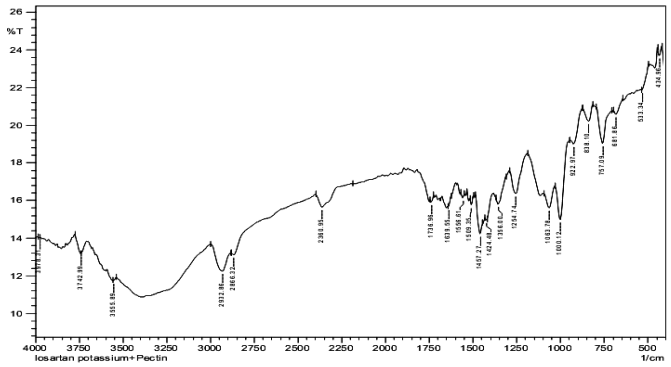

Fig. 6: FTIR OF DRUG + PECTIN

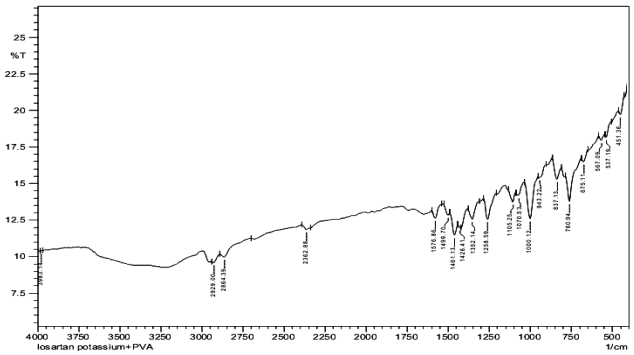

Fig. 7: FTIR OF DRUG + PVA

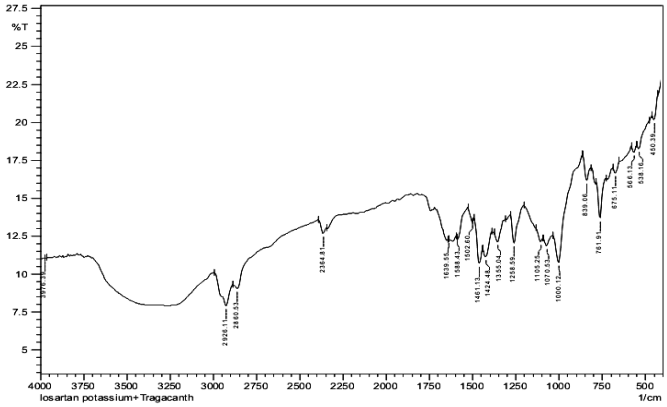

Fig. 8: FTIR OF DRUG + TRAGACANTH

SCANNING ELECTRON MICROSCOPY

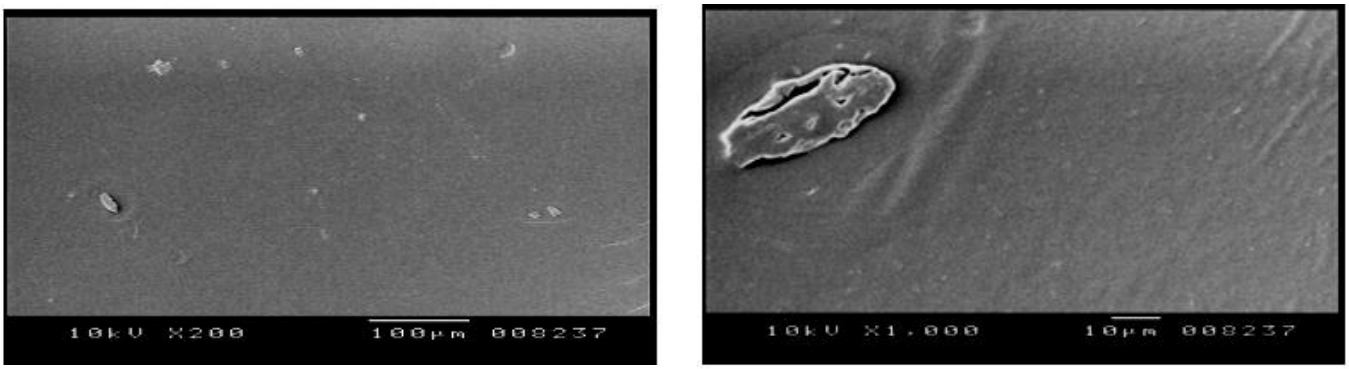

Fig. 9: Scanning electron microscopy photograph of fast dissolving film of losartan

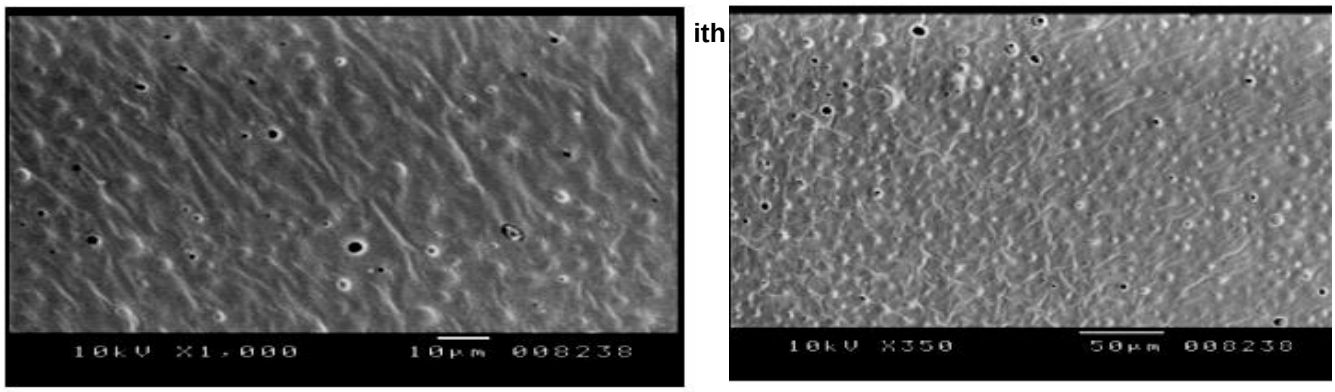

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Fig. 10: Scanning electron microscopy photograph of fast dissolving film of losartan potassium with HPMC

EVALUATION

Weight uniformity of films

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.

Moisture uptake

All the films are free from the moisture uptake and there is no evidence of Moisture attack in the prepared films and data shown in table 4.

Thickness of films

The thickness of the film was measured using vernier calipers. 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. The results of thickness for films were shown in Table 4.

Folding endurance

The folding endurance of the films was determined by repeatedly folding a Small strip of films at the same place till it breaks and the folding endurance data of all the films is given in table 4. Among all the formulations, Formulation F1 to F3 showed minimum folding Endurance time which is indicate that these fast dissolving films are excellent in Flexibility as compared to other formulations.

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

Formulation	Weight(mg)	Moisture uptake	Thickness(mm)	Folding
F1	48.00 ± 1.00	Nil	0.7 ± 0.115	112 ± 2.517
F2	47.66 ± 1.528	Nil	0.8 ± 0.057	123 ± 3.215
F3	47.21 ± 1.00	Nil	0.7 ± 0.057	123 ± 4.726
F4	50.32 ± 1.432	Nil	1.1 ± 0.010	144 ± 3.215
F5	43.10 ± 0.522	Nil	0.9 ± 0.152	133 ± 4.509
F6	47.10 ± 0.574	Nil	0.9 ± 0.200	149 ± 2.082
F7	56.25 ± 0.362	Nil	1.1 ± 0.173	171 ± 3.606
F8	57.45 ± 0.220	Nil	1.1± 0.100	184 ± 4.041
F9	60.29 ± 1.210	Nil	1.1± 0.100	197 ± 2.517
F10	49.27 ± 0.572	Nil	0.8 ± 0.057	162 ± 3.606
F11	52.14 ± 0.528	Nil	0.9 ± 0.057	133 ± 3.055
F12	56.20 ± 0.577	Nil	0.8 ± 0.100	208 ± 2.887
F13	50.12 ± 0.320	Nil	1.1 ± 0.057	201 ± 3.512
F14	51.12 ± 0.336	Nil	1.1 ± 0.100	142 ± 3.055
F15	52.29 ± 0.385	Nil	1.1 ± 0.100	141 ± 3.606

Drug content uniformity

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 given in table.

Table 5: Evaluation of Drug content uniformity

Formulation code	Drug content	In vitro	Swelling index
F1	93.91% ± 0.047	19 ± 3.606	64.65 ± 2.263
F2	92.90 ± 0.056	22 ± 1.00	60.24 ± 2.234
F3	95.94 ± 0.035	22 ± 2.517	58.33 ± 3.608
F4	91.27 ± 0.063	42 ± 2.887	65.27 ± 2.402
F5	96.65 ± 0.058	31 ± 1.000	62.22 ± 3.845
F6	91.58 ± 0.049	38 ± 2.517	56.60 ± 5.920
F7	90.06 ± 0.027	45 ± 1.051	48.66 ± 3.395
F8	89.55 ± 0.025	49 ± 2.887	52.08 ± 3.608
F9	88.33 ± 0.027	47 ± 2.646	57.77 ± 3.851
F10	91.27 ± 0.043	38 ± 2.517	63.80 ± 3.920
F11	95.63 ± 0.032	19 ± 1.528	65.79 ± 4.440
F12	90.87 ± 0.015	19 ± 1.428	54.16 ± 3.608
F13	88.84 ± 0.015	39 ± 4.00	48.88 ± 3.851
F14	96.85 ± 0.041	17 ± 1.528	69.08 ± 3.608
F15	98.68 ± 0.034	16 ± 1.528	71.16 ± 3.608

In vitro disintegration time of films

The in vitro disintegration time is calculated by the time taken by film to Under go complete disintegration. Electrolab Disintegration test apparatus (USP) may be used for this study. The disintegration time of different formulation was shown in table 5. The in vitro disintegration time of all the formulations within the range of 16 ± 1.528 to 49 ± 2.887 seconds fulfilling the official requirements. As the concentration of the super disintegrant increases the in vitro disintegration time of the film also decreases.

Swelling index

The studies for swelling index is carried out in pH 6.8 phosphate buffer solution.

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.

Time (sec)	%cumulative amount of drug release			
	F1	F2	F3	F4
0	0	0	0	0
30	26.95±0.003	20.49±0.003	19.12±0.015	22.44±0.015
60	37.87±0.035	34.31±0.005	30.39±0.011	40.20±0.012
90	59.24±0.010	57.03±0.006	51.32±0.015	56.09±0.009
120	72.10±0.005	73.60±0.008	70.01±0.014	71.09±0.005
150	88.56±0.009	85.17±0.006	86.07±0.015	89.11±0.003

Table 6: Cumulative % Drug Release (F1 – F4)

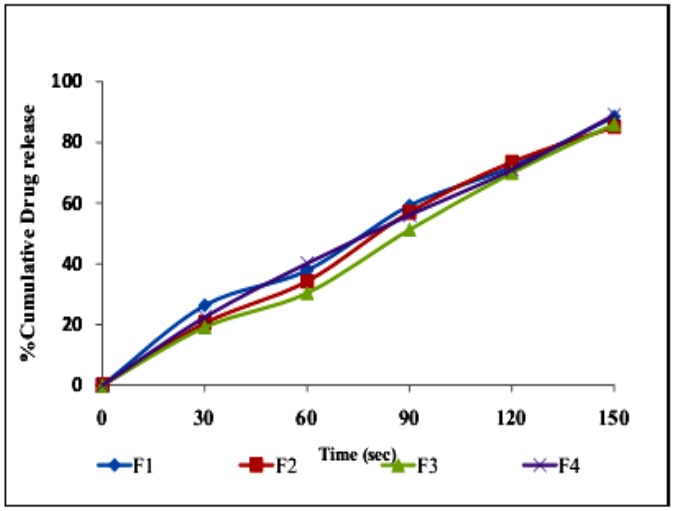

Fig. 11: Dissolution Profile of F1-F4

Time (Min)	%cumulative amount of drug release		
	F5	F6	F7
0	0	0	0
1	2.27 ± 0.005	10.69 ± 0.012	8.15 ± 0.011
2	12.27 ± 0.014	27.99 ± 0.015	26.02 ± 0.016
3	39.18 ± 0.010	45.38 ± 0.009	42.22 ± 0.009
4	61.92 ± 0.110	66.00 ± 0.012	59.10 ± 0.020
5	83.80 ± 0.120	82.43 ± 0.011	79.60 ± 0.018

Table 7: Cumulative % Drug Release (F5 – F7)

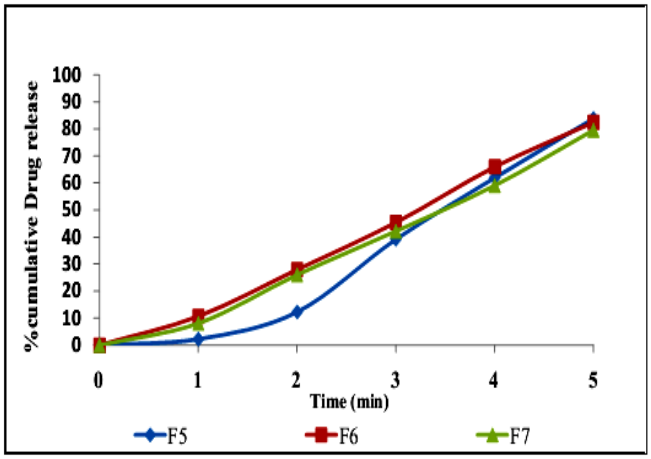

Fig. 12: Dissolution Profile of F5-F7

Time (Min)	% cumulative amount of drug release		
	F8	F9	F10
0	0	0	0
1	4.62 ± 0.010	1.06 ± 0.014	5.80 ± 0.016
2	20.51 ± 0.012	12.65 ± 0.008	18.56 ± 0.013
3	43.74 ± 0.009	37.79 ± 0.035	39.82 ± 0.010
4	60.63 ± 0.008	59.15 ± 0.009	66.68 ± 0.012
5	78.40 ± 0.011	75.54 ± 0.007	78.99 ± 0.110

Table 8: Cumulative % Drug Release (F8 – F10)

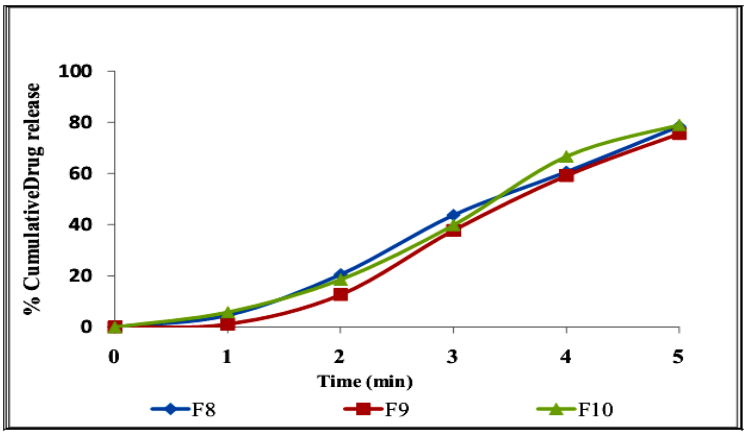

Fig. 13: Dissolution Profile of F8-F10

Time (sec)	%cumulative amount of drug release		
	F11	F12	F13
0	0	0	0
30	24.80 ± 0.012	14.22 ± 0.013	16.57 ± 0.010
60	46.68 ± 0.010	28.60 ± 0.010	29.79 ± 0.015
90	62.99 ± 0.017	49.52 ± 0.007	51.10 ± 0.012
120	79.99 ± 0.009	68.99 ± 0.009	67.84 ± 0.014
150	90.22 ± 0.011	80.14 ± 0.010	81.73 ± 0.009

Table 9: Cumulative % Drug Release (F11 – F13)

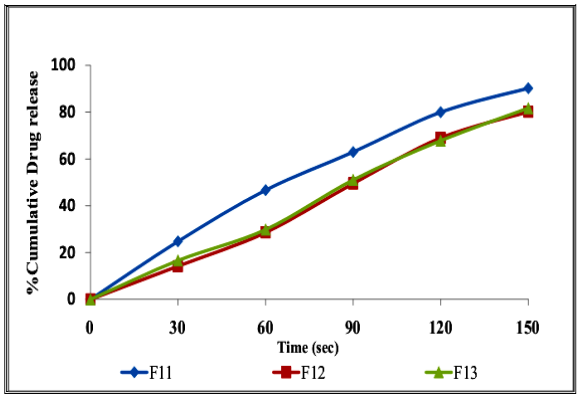

Fig. 14: Dissolution Profile of F11-F13

Time (sec)	%cumulative amount of drug release	
	F14	F15
0	0	0
30	27.34 ± 0.008	30.28 ± 0.012
60	61.77 ± 0.012	66.88 ± 0.010
90	85.42 ± 0.009	96.83 ± 0.013
120	93.14 ± 0.016	

Table 10: Cumulative % Drug Release (F14 – F15)

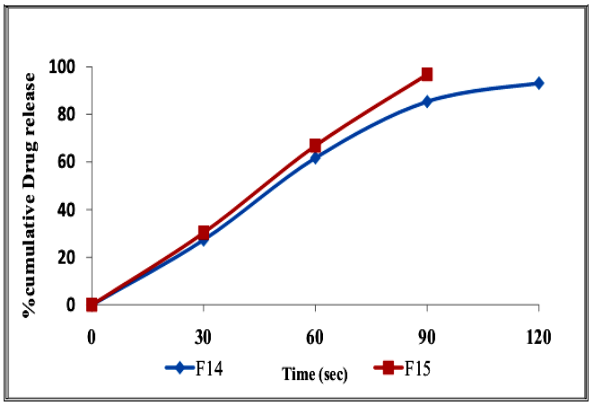

Fig. 15: Dissolution Profile of F14-F15

Stability studies

The selected formulations was evaluated for short term stability studies which was stored at 40^{0}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 the values were shown in the tables below.

Table 11: Stability data of formulation F1

Times in Months	Formulation F1 stored at 40^{0}C/ 75 % RH		
	Physical appearance	In vitro Dispersion time	% Drug content
1	+++	2.00	93.91
2	+++	2.30	92.80
3	++	2.40	92.65

Table 12: Stability data of formulation

Times in Months	Formulation F11 stored at 40^{0}C/ 75 % RH		
	Physical appearance	In vitro Dispersion time	% Drug content
1	+++	2.45	95.63
2	+++	3.10	94.50
3	++	3.20	94.10

Table 13: Stability data of formulation F15

Times in Months	Formulation F15 stored at 40^{0}C/ 75 % RH		
	Physical appearance	In vitro Dispersion time	% Drug content
1	+++	1.50	98.68
2	+++	2.30	97.45
3	++	2.45	97.10

Fig. 16: Photograph of buccal films of Propranolol HCl

CONCLUSION

In the present study fast dissolving drug delivery system of Losartan potassium were successfully developed in the form of fast dissolving oral films which offers a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with increase in patient compliance by avoiding the first pass metabolism and enhance the bioavailability of the drug.

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