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FORMULATION AND EVALUATION OF FAST DISSOLVING FILM OF LOSARTAN POTASSIUM

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ABSTRACT

Losartan potassium is a Losartan is an angiotensin-receptor blocker (ARB) used in the management of raised blood pressure. The purpose of this research work was to formulate the fast dissolving film of Losartan potassium for the treatment of hypertension, by using the polymer such as PVA and Maltodextrin in different concentration. Films of Losartan potassium were prepared by solvent casting method using the polymer such as PVA and Maltodextrin in different ratio. Films of Losartan potassium were prepared by solvent casting method using the polymer such as PVA and Maltodextrin in different ratio. Propylene glycol was used as plasticizer. Films were subjected for physicochemical characterization evaluation such as thickness, weight uniformity, folding endurance, drug content, surface pH study, in vitro drug release, ex vivo permeation study and stability study. Result: Films were found to be satisfactory when evaluated for thickness, weight uniformity, in-vitro drug release, folding endurance, drug content and disintegration time. The surface pH of all the films was found to be neutral pH. The in vitro drug release in optimized formulation F8 was found 78.62 % in 4 min. The optimized formulation F8 also showed satisfactory pH, drug content (97.12%),), ex vivo permeation (89.42%), effective in vitro drug release (97.93% in 10 min), disintegration time in 24 sec and satisfactory stability.

Key words: *Anti-hypertension drug; oral drug delivery; solvent casting technique; hydrophilic polymer; oral dissolving film.*

INTRODUCTION

Some patients have difficulties in swallowing or chewing solid dosage from which risk or fear of chocking, so this is a major problem in the use of solid dosage. Oral dissolving film is a new drug delivery system for oral drug delivery. Oral film a form is used in acute conditions such as pain, emetic, migraine, hypertension, CHF, Asthma etc. Oral dissolving film has gained popularity due to its availability in various size and shape**.** Oral dissolving films are intended to disintegrate or dissolve within seconds. They offer advantages such as administration without water, ease of swallowing, rapid onset of action and convenience of dosing. For fast dissolving active pharmaceutical ingredients, absorption is possible through the oral mucosa and may improve bioavailability.

The concept of oral dissolves film

- This delivery system consists of a thin film.

- After placing it on the top of the tongue, the film dissolves within seconds, promoting first pass metabolism as compared to tablet and other immediate release oral solid dosage forms, and may increase the bioavailability of drug.
- FDF dissolves in the mouth like a cotton candy.

Losartan competitively inhibits the binding of angiotensin II to AT1 in many tissues including vascular smooth muscle and the adrenal glands. Losartan is metabolized to its active metabolite, E-3174, which is 10 to 40 times more potent than losartan and acts as a non-competitive AT1 antagonist. Inhibition of angiotensin II binding to AT1 inhibits its AT1-mediated vasoconstrictive and aldosterone-secreting effects and results in decreased vascular resistance and blood pressure. Losartan is 1,000 times more selective for AT1 than AT2. Inhibition of aldosterone secretion may increase sodium and water excretion while decreasing potassium excretion. Losartan is effective for reducing blood pressure and may be used to treat essential hypertension, left ventricular hypertrophy and diabetic nephropathy.

Fast dissolving film as an ideal dosage form for the patients who difficult to swallow the tablet. Due to its ease of usage and high acceptability, fast dissolving films were formulated in the present study. The objective of present study was to formulate, fast dissolving film of Losartan potassium by using a combination of polymers i.e. Polyvinylalchol and Maltodextrin in different concentration; To avoid presystemic metabolism of the drug; To eliminate the patient's fear of choking with FDT, glycerin as a plasticizer , crosspovidone as a superdisintegration agent, mannitol as a sweetening agent and citric acid as a saliva stimulating agent.

MATERIALS

Losartan potassium was obtained as a gift sample from unicam, baddi, India. PVA, MD, Mannitol, citric acid and crosspovidone was purchased from S.D. Fine Chem Ltd, India. All other chemical used were analytical grade and were used without purification. Double distilled water was used in the study.

METHOD

Fast dissolving oral film were prepared by using the combination of polymers by the solvent casting technique. The hydrophilic polymers namely Maltodextrin (MD) and Polyvinylalchol (PVA) were accurately weighed and dissolved in the distilled water and propylene glycol (PG) was used as plasticizer. Drug and other ingredients were added to the polymeric dispersion under constant stirring with a magnetic stirrer and the resultant homogeneous solution was poured into a petridish, then film was dried in an oven at 50ºC for 24 h. The dried films were wrapped in butter paper then cover with aluminum foil and kept in desiccator.

EVALUATION OF FAST DISSOLVING FILMS

1. Appearance, Size, Shape and Thickness:

The formulated film was checked for their appearance, shape and thickness. The thickness of film was determined at five different places using a digimatic micrometer (Mitutoyo Co., Japan) for each formulation and mean value was calculated.

2. Weight variation:

The patches were subjected to mass variation study by individually weighing randomly selected patches. The average of five observations of each batch was calculated. Such determinations were carried out for each batch.

3. Drug Content:

The film of specified area (2×2cm) was cut and added to a volumetric flask containing 100 ml of phosphate buffer pH 6.8. The medium was stirred on a magnetic stirrer for proper dissolution for 6 hours. The contents were filtered using Whatman filter paper and the filtrate was analyzed by UV spectrophotometer (Pharmaspec-1700S, Shimadzu, Japan) at 206 nm. The experiment was performed in triplicate.

4. Folding Endurance:

It was determined by repeatedly folding a small strip of the patch (2×2cm) at the same place till it broke. The number of times a film can be folded at the same place without breaking gave the value of folding endurance. Further, less folding endurance value indicates more brittleness.

5. Disintegration time:

In-vitro disintegration time was determined visually in a petri dish containing 25 ml of pH 6.8 phosphate buffer with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates.

6. *In-vitro* drug release:

For *in-vitro* dissolution studies, each film was placed with the help of forceps in a 50 ml glass beaker containing 25 ml of phosphate buffer pH6.8. The temperature of the dissolution media was maintained at 37±0.5ºC; 50 rpm. During the study, 3ml of aliquots were withdrawn at 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 minute and were replaced by fresh buffer. The amount of drug release in the media was determined by a UV-Visible Spectrophotumeter (Shimadzu 160 A, Kyoto, Japan) at 206 nm.

7. *Ex-vivo* permeation studies:

Ex- vivo skin permeation study was performed by using a Franz diffusion cell with a receptor compartment capacity of 13 ml. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 6.8. Porcine oral mucosa membrane was mounted between the donor and receptor compartment. The formulated film of 2×2cm diameter was cut and placed over the porcine oral mucosa membrane. The donor compartment was then placed and fixed over it with the help of rubber bandages. The whole assembly was placed on magnetic stirrer, and the solution in the receptor compartment was continuously stirred. The temperature was maintained at 37 ± 2ºC. The samples of 1 ml were withdrawn at time interval of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 min and were analyzed at 206 nm spectrophotometrically for drug content against blank. The receptor phase was replenished with an equal volume of phosphate buffer each time the sample was withdrawn. The percentage of the released drug was calculated and plotted against time.

8. Stability studies:

The stability studies were conducted by storing the formulated fast dissolving film at 40 ± 2ºC/75% RH in stability chamber (MAR® Environmental test chamber, CAT No. MSW-127) for 45 days. The samples were withdrawn after 45 days and analyzed for drug content.

RESULT AND DISSCUSION

The prepared films were smooth, transparent, flexible and uniform. The films were casted in 10 cm diameter petridish. For evaluation purposes 2 cm^2 area was cut from it. The thickness of the film varied from 0.17±0.006 to 0.30 ± 0.071 mm. The standard deviation values were low indicating uniformity in thickness as shown in table 2.
Variation in weight of the formulation was determined by weighing 2 cm^2 section of each film on a digital balance and then calculating the average weight. From the results shown in table 2; it was observed that all the batches were uniform in weight with no significant difference in the weight of the individual formulation from the average value. Weight variation was found to be in range of 0.082 ± 0.002 to 0.189 ± 0.006 mg for films prepared.

The folding endurance was measured manually. It measures the ability of film to withstand rupture. The results indicated that the endurance increases on increasing polymer content in the film. It varied from 341.66± 2.51 to 570.66 ± 2.08 in the films formulated as shown in table 2.

Drug content of all the formulations was determined using UV-Visible spectrophotometer. The result showed good uniformity of drug content throughout the films without any significant variation as shown in table 2. Drug content was found to vary from 86.62 ± 0.5 to 98.14± 0.64 in films.

The surface pH of the films was ranging from 6.5 ± 0.27 to 6.88 ± 0.32 as shown in table 2. Since the surface pH of the films was found to be around the neutral pH, there will not be any kind of irritation to the mucosal lining of the oral cavity.

It was observed that in vitro disintegration time varies from 8.33±1.52 to 43±1 sec for all the formulations as shown in table: 2. In vitro disintegration time of FDFs containing PVA and maltodextin as polymer was affected by the thickness of the film. In vitro disintegration time of the films was found to increase with increase in the amount of the polymer.

A phase contrast microscopy photograph of the film gives an idea about the surface topology and less precisely about the drug distribution pattern. Fig 6 shows the phase contrast microscopy photograph of the best formulated batch F8 and F10. It exhibited smooth surface having homogeneous distribution of the drug throughout the film.

From the release kinetic results, most of the formulations were demonstrated zero order kinetic release pattern. Stability studies conducted as per ICH guidelines at 40º C / 75% RH indicated that there is no decrease in drug content or no significant difference between the mean of profile. Thus, the manufactured fast dissolving films were found to be stable with respect to physiochemical and release characteristics. From all the above results formulation F8 was found to be best formulation for the fast dissolving drug delivery of Losartan potassium that complied with all parameters.

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Table 1: **Formulation Table of Losartan Potassium Loaded Oral Films**

Batch Code	PVA (mg)	MD (mg)	PG (ml)	D.W	Citric acid (mg)	Cross Povidone (mg)	Mannitol (mg)	Drug (mg)
F1	200	200	1	q.s.	20	20	20	450
F2	250	200	1	q.s.	20	20	20	450
F3	300	200	1	q.s.	20	20	20	450
F4	300	100	1	q.s.	20	20	20	450
F5	400	200	1	q.s.	20	20	20	450
F6	500	200	1	q.s.	20	20	20	450
F7	200	250	1	q.s.	20	20	20	450
F8	250	250	1	q.s.	20	20	20	450
F9	300	250	1	q.s.	20	20	20	450
F10	200	300	1	q.s.	20	20	20	450
F11	250	300	1	q.s.	20	20	20	450
F12	300	300	1	q.s.	20	20	20	450

Quantity of drug was calculated as per the area of Petridis, so that each film 2×2 cm will contain 25 mg of drug.

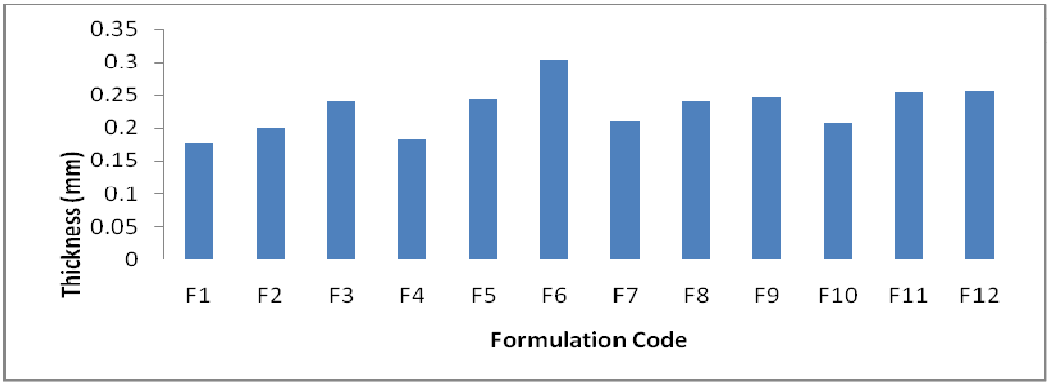

Fig. 1: Comparative Evaluation of Thickness of All Film Formulations

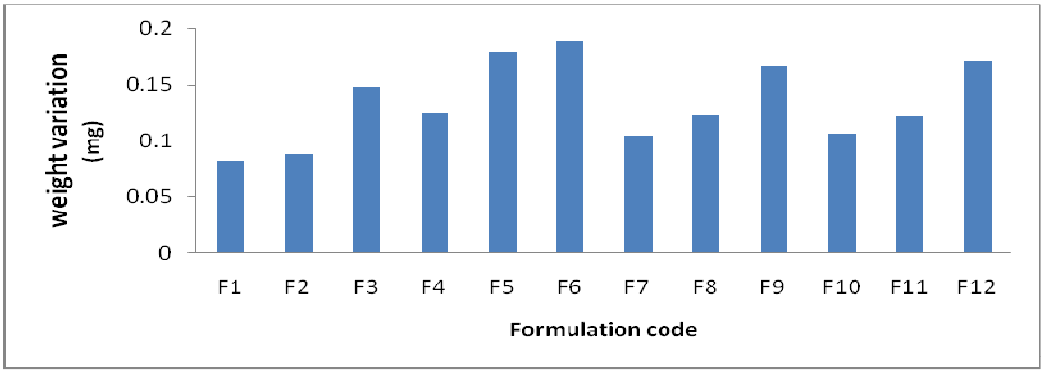

Fig. 2: Comparative Evaluation of Weight Variation of All Formulations

Table 2: Evaluation Results of Fast Dissolving Film

Formulation Code	Thickness (mm)	Weight Variation (mg)	Folding Endurance	Disintegration Time (sec)	%Drug Content	Surface pH
F1	0.17±0.006	0.082±0.002	341.66±2.51	8.33±1.52	98.14±0.64	6.5±0.27
F2	0.20±0.01	0.088±0.003	348.66±1.52	17.66±1.15	86.62±0.50	6.56±0.18
F3	0.24±0.01	0.124±0.001	388.33±1.52	24.33±0.57	97.57±0.91	6.69±0.18
F4	0.18±0.005	0.106±0.005	427.33±0.57	19.66±1.52	96.77±1.20	6.72±0.30
F5	0.24±0.030	0.178±0.003	461.33±1.15	38.66±0.57	95.27±3.84	6.68±0.22
F6	0.30±0.071	0.189±0.006	472±1	43±1	97.68±0.88	6.52±0.40
F7	0.21±0.01	0.105±0.008	479.66±1.52	12.66±1.15	94.89±1.49	6.66±0.15
F8	0.24±0.01	0.124±0.001	527±1.73	24.66±0.57	97.12±0.54	6.78±0.12
F9	0.25±0.015	0.166±0.003	570.66±2.08	30±1	93.85±0.19	6.79±0.12
F10	0.20±0.020	0.122±0.002	357.33±1.15	16.66±0.57	96.42±0.57	6.82±0.09
F11	0.25±0.006	0.148±0.002	332.33±0.57	19.33±0.57	97.25±0.58	6.73±0.22
F12	0.25±0.015	0.171±0.015	543.66±1.15	32.66±1	95.27±0.46	6.88±0.32

Table 3: *In-vitro* drug release data of all formulations of Losartan potassium fast dissolving film

Time (sec)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
60	47.31	45.38	44.17	39.98	49.55	46.27	45.72	56.34	47.72	62.06	54.69	47.31
120	51.72	49.17	50.26	53.55	59.29	48.96	63.45	66.89	54.62	64.27	56.82	51.72
180	54.27	53.52	55.35	56.72	66.88	56	65.24	69.31	61.52	69.24	62.48	54.27
240	57.65	54.96	60.07	62.16	69.75	58.68	67.31	78.62	65.31	72.68	65.03	57.65
300	63.86	57.1	65.26	66.7	75.73	63.79	68.2	79.31	67.51	79.03	68	63.86
360	67.79	59.03	67.42	77.28	78.53	66.55	69.24	80.68	74.48	80.55	75.34	67.79
420	77.03	61.86	72.56	80.75	83.55	68.2	78.69	87.79	76.82	81.79	78	77.03
480	79.51	64.41	77.28	83.55	83.74	76	79.79	90.55	84.2	82.75	85.24	79.51
540	85.44	67.79	81.05	84.63	84.81	80.13	82.14	96.82	91.03	85.26	90.96	85.44
600	90.27	76.06	87.8	88.69	86.25	85.86	83.59	97.93	97.31	99.86	97.38	90.27

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Table 4: *Ex-vivo* Drug Permeation Data of Formulations F8 and F10 of Losartan Potassium Fast Dissolving Films

TIME (min.)	FORMULATION CODE	
	F8	F10
0	0	0
1	53.37	39.98
2	57.73	53.55
3	67.42	56.72
4	72.62	62.16
5	78	66.7
6	83.55	77.28
7	85.41	80.75
8	88.82	83.55
9	88.93	84.63
10	89.42	88.69

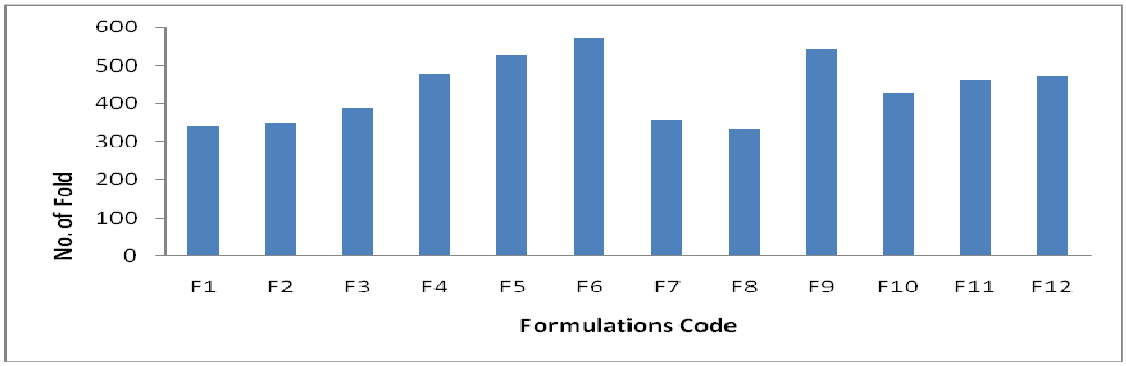

Fig 3: Comparison of Folding Endurance of All Film Formulations

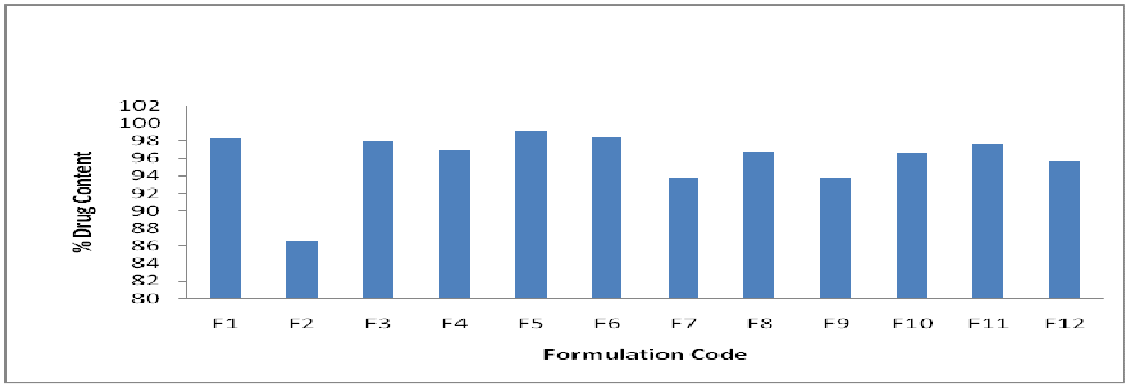

Fig. 4: Result of the Drug Content of Film Formulations

Table: 5: Release Kinetics of Losartan Potassium Fast Dissolving Films

FORM.	HIGUCHI		HIXON		FIRST ORDER		ZERO ORDER		KORESMAYER		
	R^2	K	R^2	K	R^2	K	R^2	K	R^2	K	n
F1	0.944	2.651	0.954	-0.002	0.923	-0.001	0.987	0.081	0.858	0.642	1.253
F2	0.925	1.586	0.927	-0.001	0.905	-0.000	0.960	0.048	0.871	0.441	1.377
F3	0.981	2.515	0.973	-0.002	0.945	-0.001	0.076	0.995	0.938	0.654	1.234
F4	0.981	2.906	0.982	-0.003	0.982	-0.001	0.953	0.086	0.975	0.779	1.142
F5	0.970	2.205	0.955	-0.002	0.970	-0.001	0.906	0.064	0.993	0.559	1.368
F6	0.959	2.325	0.960	-0.002	0.933	-0.001	0.987	0.071	0.896	0.597	1.279
F7	0.913	1.984	0.921	-0.002	0.933	-0.000	0.871	0.058	0.93	0.531	1.373
F8	0.979	2.421	0.946	-0.003	0.911	-0.002	0.964	0.072	0.958	0.530	1.432
F9	0.962	2.824	0.900	-0.003	0.802	-0.001	0.988	0.086	0.919	0.666	1.260
F10	0.895	1.925	0.646	-0.003	0.456	-0.002	0.919	0.058	0.846	0.405	1.529
F11	0.930	2.547	0.883	-0.003	0.788	-0.001	0.982	0.079	0.836	0.556	1.368
F12	0.944	2.651	0.954	-0.002	0.923	-0.001	0.987	0.081	0.858	0.642	1.253

Table 6: Stability Study for Formulation F8

Parameter	**Initial**	**After 45 days on 40°C 75% RH**
Appearance	White	White
Thickness	0.24±0.001 mm	0.23±0.003 mm
Weight Variation	0.124±0.001 mg	0.123±0.008 mg
Folding Endurance	527±1.75	526±0.57
Disintegration Time	24.66±0.57 sec	23.66±0.66 sec
% Drug Content	97.12±0.54	97.04±0.07
Surface pH	6.78±0.12	6.76±0.012
In-vitro Drug Release	97.73% DR in 10 min	97.11% DR in 10 min

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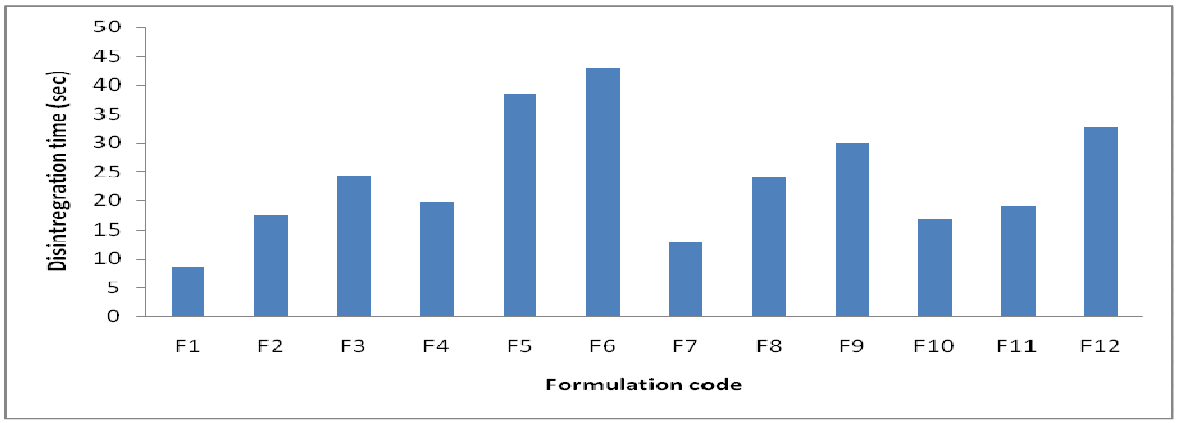

Fig. 5: **Comparative Evaluation of disintegration of formulations**.

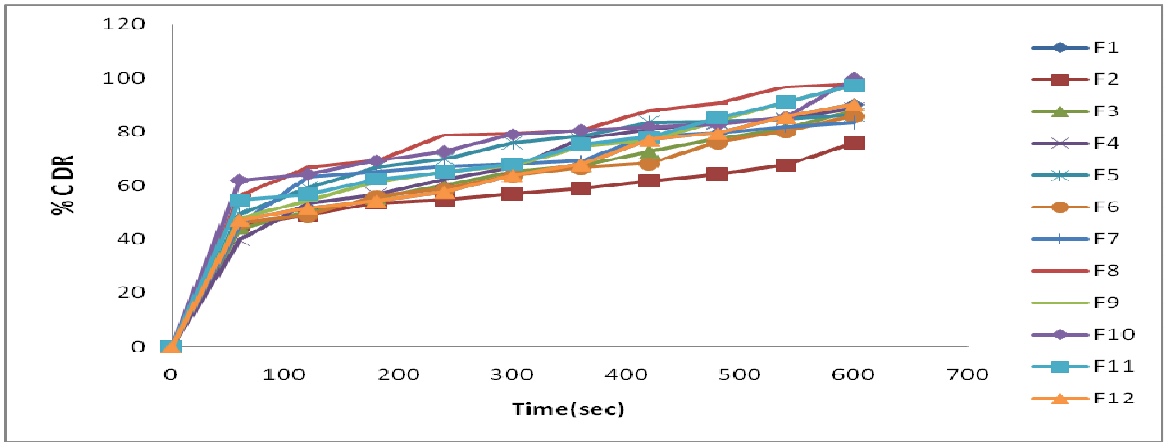

Fig. 6: ***In-vitro*** **% CDR profile of fast dissolving films showing comparative study**

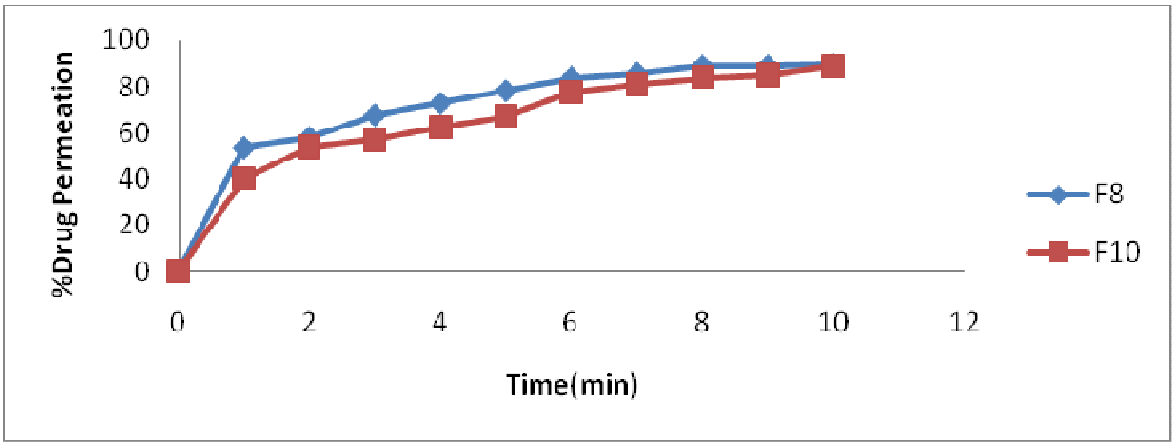

Fig. 7: ***Ex-vivo*** **Permeation Study of Formulation F8 and F10**

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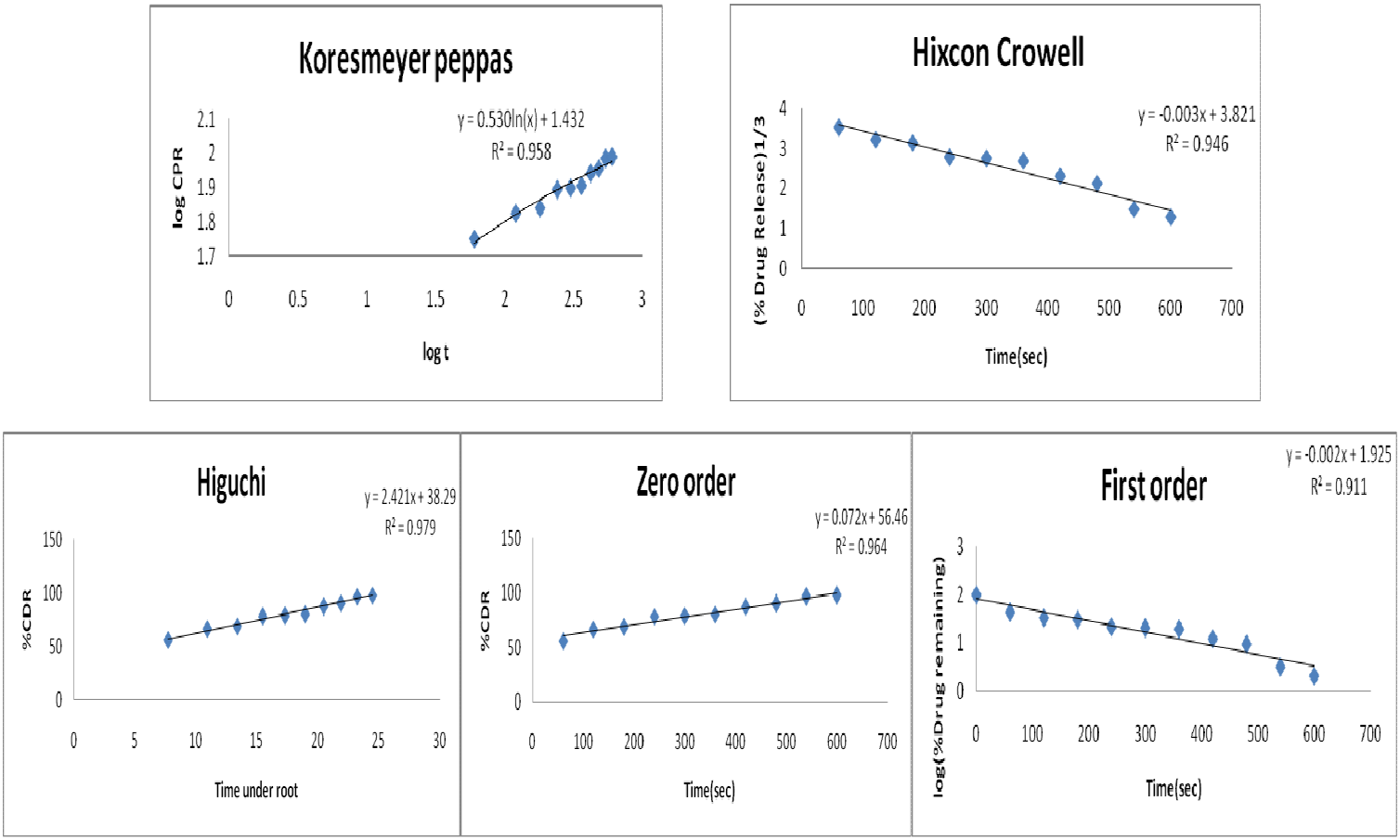

Fig: 8 Releases Kinetic For Formulation 8

CONCLUSION

It can be concluded that, fast dissolving film-containing Losartan potassium can be prepared by solvent casting method.

Fast dissolving film of formulation can be a potential novel drug dosage form for pediatric, geriatric and also for general population.

FUTURE ASPECT

- The further *in-vivo* study can be carried out in animal for better prediction of *in-vivo* behavior of the system.
- Bioavailability studies can be conducted to assess the relative usefulness of these formulations.

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