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Research Article

FORMULATION AND EVALUATION OF FAST DISSOLVING FILM OF AN ANTIHYPERTENSIVE DRUG

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ABSTRACT

Losartan potassium is an angiotensin-receptor blocker (ARB) used in the management of hypertension. The purpose of this research work was to formulate a fast dissolving film of Losartan potassium for the treatment of hypertension, by using polymers such as PolyVinylAlcohol (PVA) and Maltodextrin (MD) in different concentrations. Films of Losartan potassium were prepared by solvent casting method using polymers such as PVA and Maltodextrin in different ratios. Propylene glycol was used as a plasticizer. Films were subjected to physicochemical characterization such as thickness, weight uniformity, folding endurance, drug content, surface pH study, *in vitro* drug release, *ex vivo* permeation study and stability studies. 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. The *in vitro* drug release in optimized formulation F8 was found to be 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 (98.99% in 10 min), disintegration time of 24 seconds and satisfactory stability.

Keywords: Anti-hypertensive Drug, FDF, Solvent Casting Technique, Hydrophilic Polymer.

INTRODUCTION

Some patients have difficulty in swallowing or chewing solid dosage forms which risk or fear of chocking and thus is a major problem in the use of solid dosage forms.[1-2] Fast dissolving film (FDF) is a new drug delivery system for oral drug delivery. FDF is used in acute conditions such as pain, emesis, migraine, hypertension, congestive heart failure, asthma etc. FDF has gained popularity due to its availability in various sizes and shapes**.** These 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.[3-12]

The concept of oral dissolving film:[13-14]

- 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.
- This dissolves in the mouth like a cotton candy.

Losartan competitively inhibits the binding of angiotensin II to angiotensin I 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 angiotensin I antagonist. Inhibition of angiotensin II binding to angiotensin I inhibits its angiotensin I-mediated vasoconstrictive and aldosterone-secreting effects and results in decreased vascular resistance and blood pressure. Losartan is 1,000 times more selective for angiotensin I than

angiotensin II. Inhibition of aldosterone secretion may increase sodium and water excretion while decreasing potassium excretion. It is effective for reducing blood pressure and may be used to treat essential hypertension, left ventricular hypertrophy and diabetic nephropathy.[14-17]

FDF is an ideal dosage form for patients for whom it is difficult to swallow tablets. Due to their 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. PVA and Maltodextrin in different concentrations; glycerin as a plasticizer, crosspovidone as a superdisintegrating agent, mannitol as a sweetening agent and citric acid as a saliva stimulating agent to avoid presystemic metabolism of the drug and to eliminate patient's fear of choking with fast dissolving tablets.[18-22]

MATERIALS

Losartan potassium was obtained as a gift sample from Unicam, Baddi, India. PVA, maltodextrin, mannitol, citric acid and crosspovidone were purchased from S.D. Fine Chem Ltd, India. All other chemicals used were analytical grade and were used without purification. Double distilled water was used in the study.

METHOD

Fast dissolving oral films were prepared by using a combination of polymers by solvent casting technique. The formulations were prepared as per table no.1. The hydrophilic polymers namely Maltodextrin (MD) and Polyvinylalchol (PVA) were accurately weighed and dissolved in distilled water and propylene glycol (PG) was added as a 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 the films were dried in an oven at 50ºC for 24 h. The dried films were wrapped in a butter paper, covered with an aluminum foil and kept in a desiccator.[23-54]

EVALUATION OF FAST DISSOLVING FILMS

1 Appearance, Size, Shape and Thickness:

The formulated films were checked for their appearance, shape and thickness. The thickness of the films was determined at five different places using a digimatic micrometer (Mitutoyo Co., Japan) for each formulation and mean value was calculated.[55]

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.[56-58]

3 Drug Content

The film of specified area (2×2cm) was cut and put in 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 experiments were performed in triplicate.[56, 57, 59]

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. [57, 60-61]

5 Disintegration time

In-vitro disintegration time was determined visually in a petridish 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 disintegrate. [60-61]

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 pH 6.8. 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 minutes and were replaced by fresh buffer. The amount of drug release in the media was determined by a UV-Visible Spectrophotometer (Shimadzu 160 A, Kyoto, Japan) at 206 nm.[58]

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 a magnetic stirrer, and the solution in the receptor compartment was continuously stirred. The temperature was maintained at 37 ± 2ºC. Samples of 1 ml were withdrawn at time intervals of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 minutes 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.[55]

8 Stability studies

The stability studies were conducted by storing the formulated FDF 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 a 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 and figure 1.

Variation in the weights of the formulations 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 the range of 0.082 ± 0.002 to 0.189 ± 0.006 mg for films prepared. A graphical presentation is shown in figure 2.

The folding endurance was measured manually. It measures the ability of the 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 and figure 3.

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 and figure 4. Drug content was found to vary from 86.62 ± 0.5 to 98.14± 0.64 mg in films.

The surface pH of the films ranged from 6.5 ± 0.27 to 6.88 ± 0.32 as shown in table 2 and figure 5. 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 and figure 6. *In vitro* disintegration time of FDFs containing PVA and Maltodextin as polymers was affected by the thickness of the film. *In vitro* disintegration time of the films was found to increase with an increase in the amount of the polymer.

In-vitro drug release study was performed up to 600 seconds. *In-vitro* drug release studies showed that drug get rapidly released from all formulations. Maximum *in-vitro* release was found to be 98.99 % over a period of 10 min in batch F8 while minimum *in-vitro* release was found to be 76.06 % in batch F2. The results for release studies are shown in table 3. The graph was plotted between cumulative percentage drug release and time and shown in figure 7.

Ex-vivo permeation study was performed on the two formulations i.e. F8 and F10 because they give the maximum drug release among all formulations. *Ex-vivo* permeation of drug from F8 was slightly higher than F10. The percentage of the drug permeated was calculated and plotted against time and the results are shown in table 4 and figure 8.

Kinetic studies i.e. Zero-order, First order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models were fitted for all formulations. The values of regression correlation co-efficient (R^2), rate constant K and n were evaluated for all the formulations. The results are tabulated in table 5.

It is evident that all the formulations did not follow a zero order profile of drug release based on the lower R^2 values obtained compared to the other four kinetic models examined. The first order plot was found to be fairly linear as indicated by their high regression value (0.8296 to 0.9733). Value of R^2 for first order kinetic equations were greater than zero order kinetics for all the formulations indicating that the release from the films was dependent on the concentration of drug present in the formulation.

On the other hand, the R^2 values obtained from examining the first order, Higuchi, Hixson-Crowell and the Korsmeyer-Peppas models were found to be very close to each other throughout the whole series of formulations investigated. The data was fitted with Higuchi equation which yielded almost linear plots with highest regression co-efficient (0.8724 to 0.9869) indicating the mechanism of drug release was diffusion. The dissolution data was

also plotted in accordance with Hixson Crowell cube root law. Linearity of data indicates a change in surface area with the progressive dissolution of matrix as a function of time. To know precisely whether fickian or non fickian diffusion existed, the korsmeyer's peppas equation data was analyzed. Values of n for all the formulations ranged from 0.1982 to 0.3793 indicating the Fickian mechanism of release. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient.

The observations showed that mechanism of drug release for all the formulation was fickian diffusion following first order kinetics and Higuchi model of drug release.

CONCLUSION

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. The *in vitro* drug release in optimized formulation F8 was found to be 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 (98.99% in 10 min), disintegration time of 24 seconds and satisfactory stability.

Fast dissolving film 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.

Table 1: **Formulation Table of Losartan Potassium Loaded Fast Dissolving Films**

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

Quantity of drug was calculated as per the area of petridish, so that each film 2×2 cm^2 contained 25 mg of drug.

Table 2: Evaluation Results of Fast Dissolving Films

Formulation Code	Thickness (mm)	Weight Uniformity (mg)	Folding Endurance	%Drug Content	Surface pH	Disintegration Time (sec)
F1	0.17±0.006	0.082±0.002	341.66±2.51	98.14±0.64	6.50±0.27	8.33±1.52
F2	0.20±0.01	0.088±0.003	348.66±1.52	86.62±0.50	6.56±0.18	17.66±1.15
F3	0.24±0.01	0.124±0.001	388.33±1.52	97.57±0.91	6.69±0.18	24.33±0.57
F4	0.18±0.005	0.106±0.005	427.33±0.57	96.77±1.20	6.72±0.30	19.66±1.52
F5	0.24±0.030	0.178±0.003	461.33±1.15	95.27±3.84	6.68±0.22	38.66±0.57
F6	0.30±0.071	0.189±0.006	472.00±1.00	97.68±0.88	6.52±0.40	43.00±1.00
F7	0.21±0.01	0.105±0.008	479.66±1.52	94.89±1.49	6.66±0.15	12.66±1.15
F8	0.24±0.01	0.124±0.001	527.00±1.73	97.12±0.54	6.78±0.12	24.66±0.57
F9	0.25±0.015	0.166±0.003	570.66±2.08	93.85±0.19	6.79±0.12	30.00±1.00
F10	0.20±0.020	0.122±0.002	357.33±1.15	96.42±0.57	6.82±0.09	16.66±0.57
F11	0.25±0.006	0.148±0.002	332.33±0.57	97.25±0.58	6.73±0.22	19.33±0.57
F12	0.25±0.015	0.171±0.015	543.66±1.15	95.27±0.46	6.88±0.32	32.66±1.00

Table 3: In-vitro Drug Release Data of Losartan potassium fast dissolving films

Time (min)	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
1	47.31	45.38	44.17	39.98	49.55	46.27	45.72	57.88	42.18	56.68	54.69	46.66
2	51.72	49.17	50.26	53.55	59.29	48.96	63.45	63.34	49.9	62.45	56.82	52.02
3	54.27	53.52	55.35	56.72	66.88	56	65.24	67.78	55.56	67.79	62.48	54.53
4	57.65	54.96	60.07	62.16	69.75	58.68	67.31	72.24	66.64	72.45	65.03	56.51
5	63.86	57.1	65.26	66.7	75.73	63.79	68.2	75.33	71.22	76.65	68.00	64.4
6	67.79	59.03	67.42	77.28	78.53	66.55	69.24	80.54	78.84	81.76	75.34	68.81
7	77.03	61.86	72.56	80.75	83.55	68.2	78.69	84.98	81.16	86.02	78.00	76.34
8	79.51	64.41	77.28	83.55	83.74	76.00	79.79	90.56	87.78	88.89	85.24	79.47
9	85.44	67.79	81.05	84.63	84.81	80.13	82.14	95.55	93.39	94.43	90.96	85.51
10	90.27	76.06	87.8	88.69	86.25	85.86	83.59	98.99	97.77	98.87	97.38	91.11

Table 4: Ex-vivo Drug Permeation Data of Formulations F8 and F10 of Losartan Potassium Fast Dissolving Films (expressed as %)

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

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

Code	Zero order		First order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas		
	K_0	R^2	K_1	R^2	K_H	R^2	K_{HC}	R^2	K_{KP}	R^2	N
F1	6.7536	0.8148	0.1911	0.9376	25.326	0.9486	0.2022	0.9307	2.3480	0.8999	0.2900
F2	4.8765	0.6716	0.0983	0.8296	19.315	0.8724	0.1187	0.7861	2.3131	0.9041	0.1982
F3	6.4486	0.7994	0.1669	0.9421	24.497	0.9551	0.1831	0.9224	2.4032	0.9653	0.2929
F4	7.0475	0.8141	0.1962	0.9733	26.734	0.9698	0.2095	0.9421	2.4945	0.9830	0.3454
F5	6.2524	0.6813	0.147	0.9122	25.029	0.9039	0.1863	0.8434	1.9943	0.9908	0.2467
F6	6.1648	0.7779	0.1536	0.9266	25.526	0.9379	0.1710	0.9015	2.3485	0.9308	0.2684
F7	5.8316	0.6602	0.1843	0.8749	23.402	0.8802	0.1638	0.8129	2.0488	0.9210	0.2332
F8	6.9999	0.7329	0.3447	0.8441	27.213	0.9171	0.2811	0.9167	1.8416	0.9413	0.2366
F9	7.9157	0.8672	0.3099	0.9045	29.348	0.9869	0.2818	0.9656	2.5310	0.9807	0.3793
F10	7.0040	0.7343	0.3304	0.8476	27.286	0.9227	0.2749	0.9191	1.8650	0.9639	0.2437
F11	6.8963	0.7706	0.2664	0.8377	26.253	0.9245	0.2442	0.8970	2.0276	0.8806	0.2518
F12	6.8111	0.8199	0.1955	0.9319	25.494	0.9510	0.2055	0.9318	2.3664	0.9037	0.2953

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

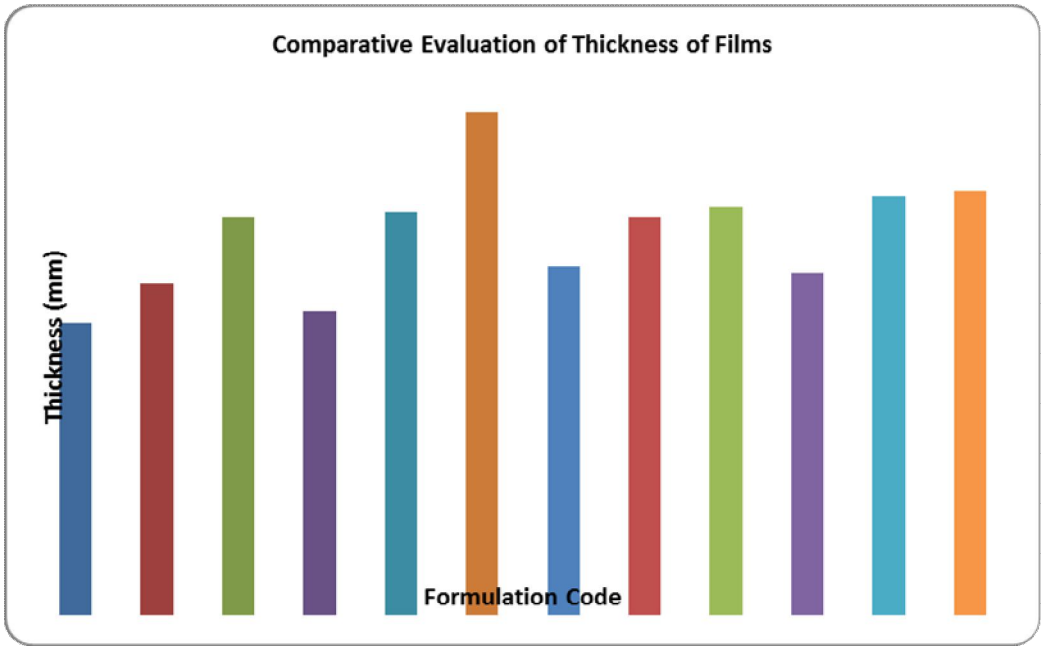

Fig. 1: Comparative Evaluation of Thickness of All Film Formulations

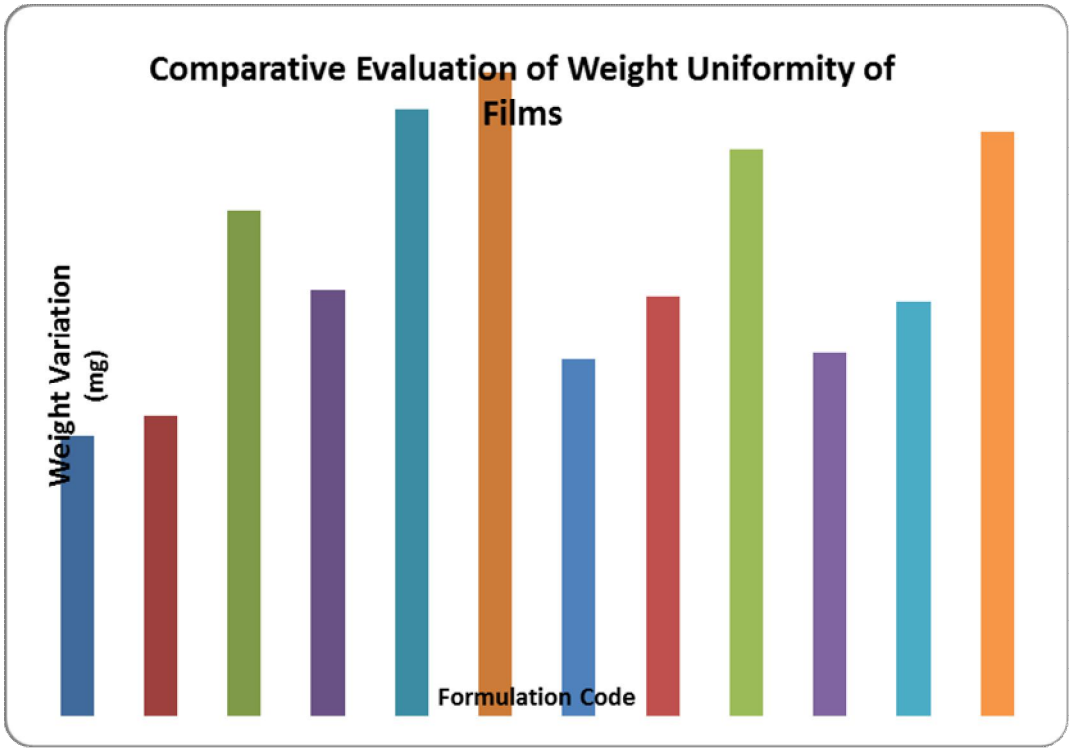

Fig. 2: Comparative Evaluation of Weight Variation of All Formulations

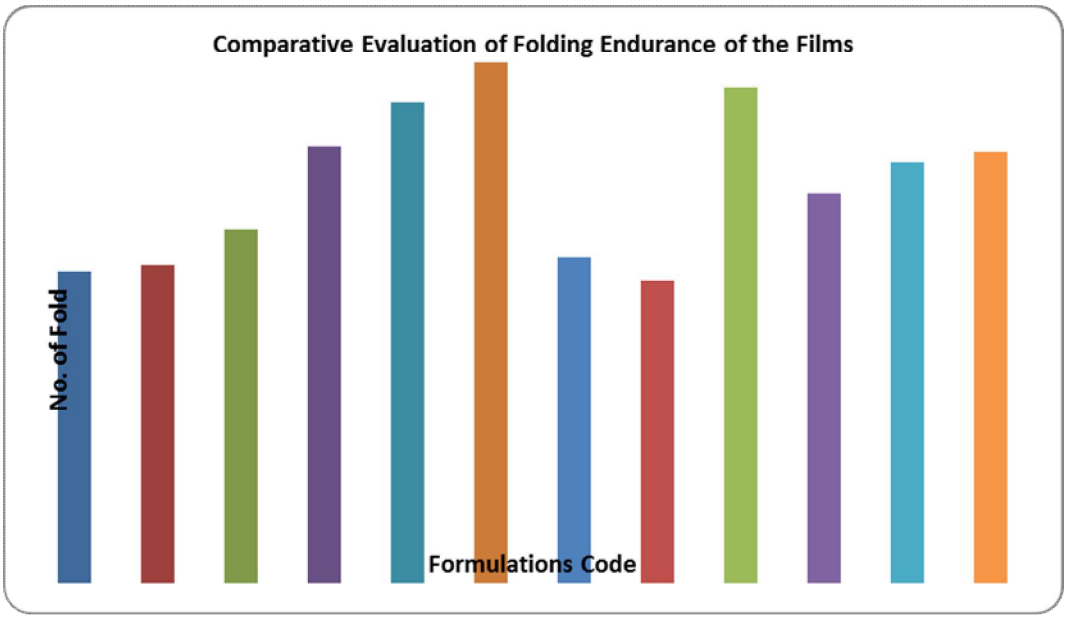

Fig. 3: Comparison of Folding Endurance of All Film Formulations

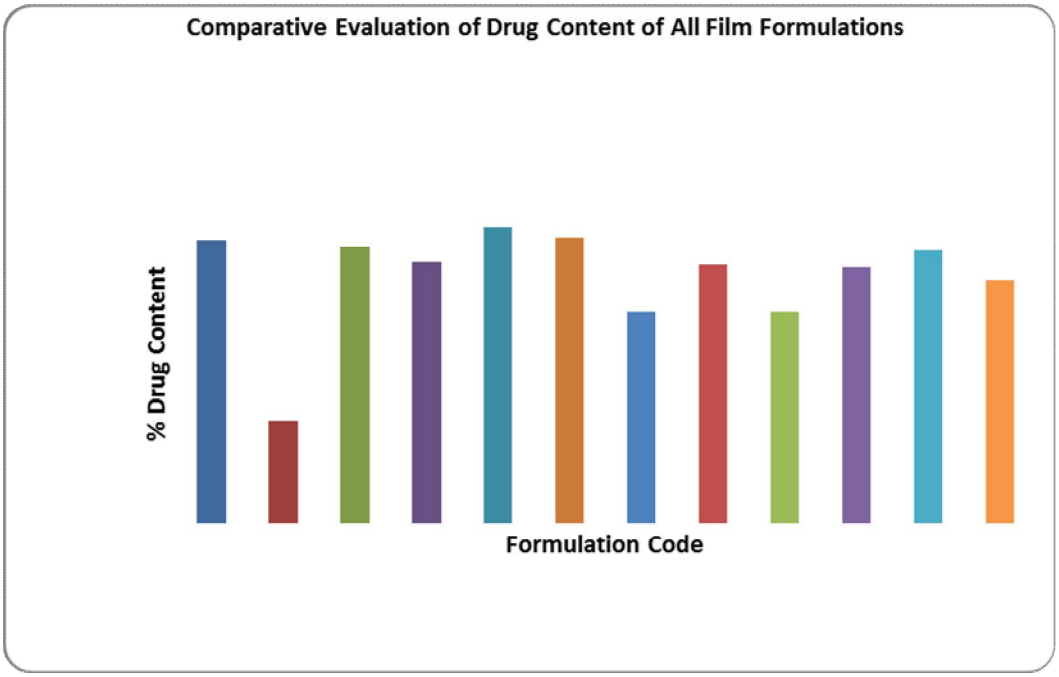

Fig. 4: Result of the Drug Content of Film Formulations

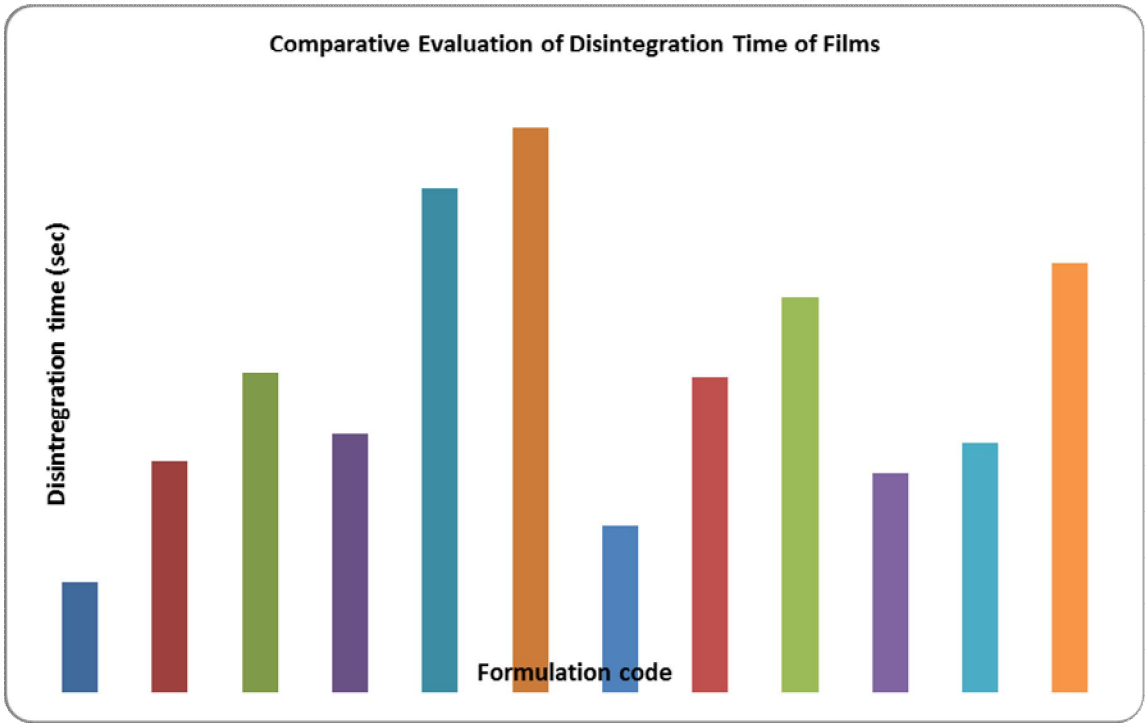

Fig. 5: Comparative Evaluation of disintegration of formulations

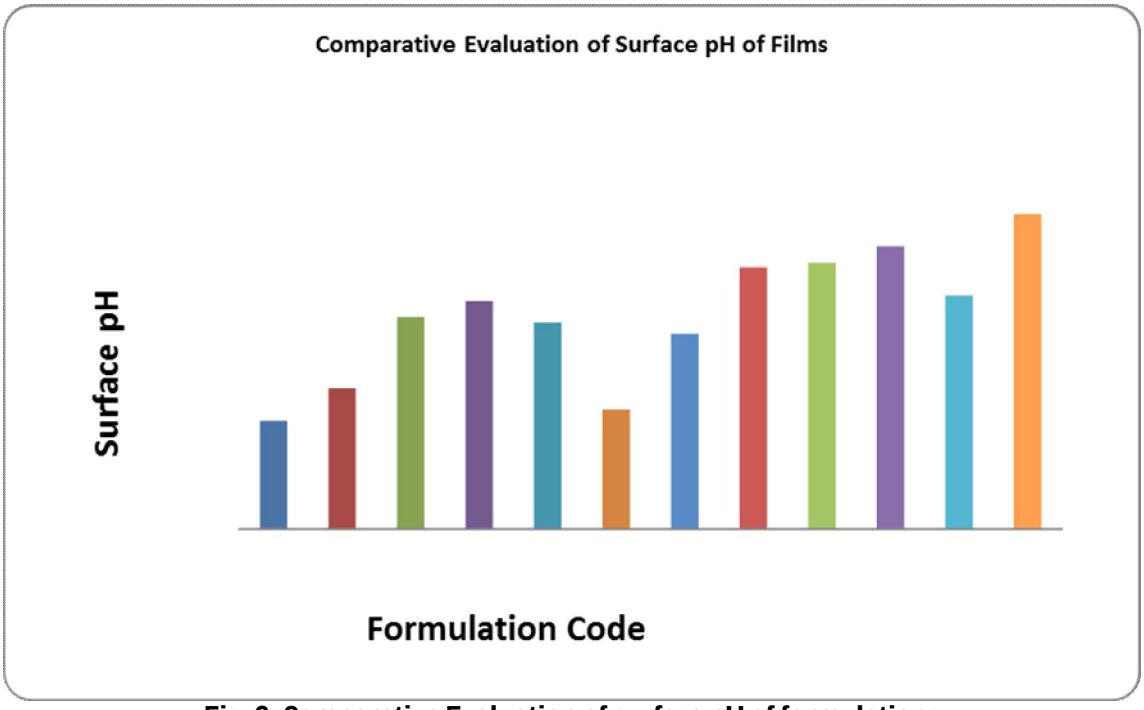

Fig. 6: Comparative Evaluation of surface pH of formulations

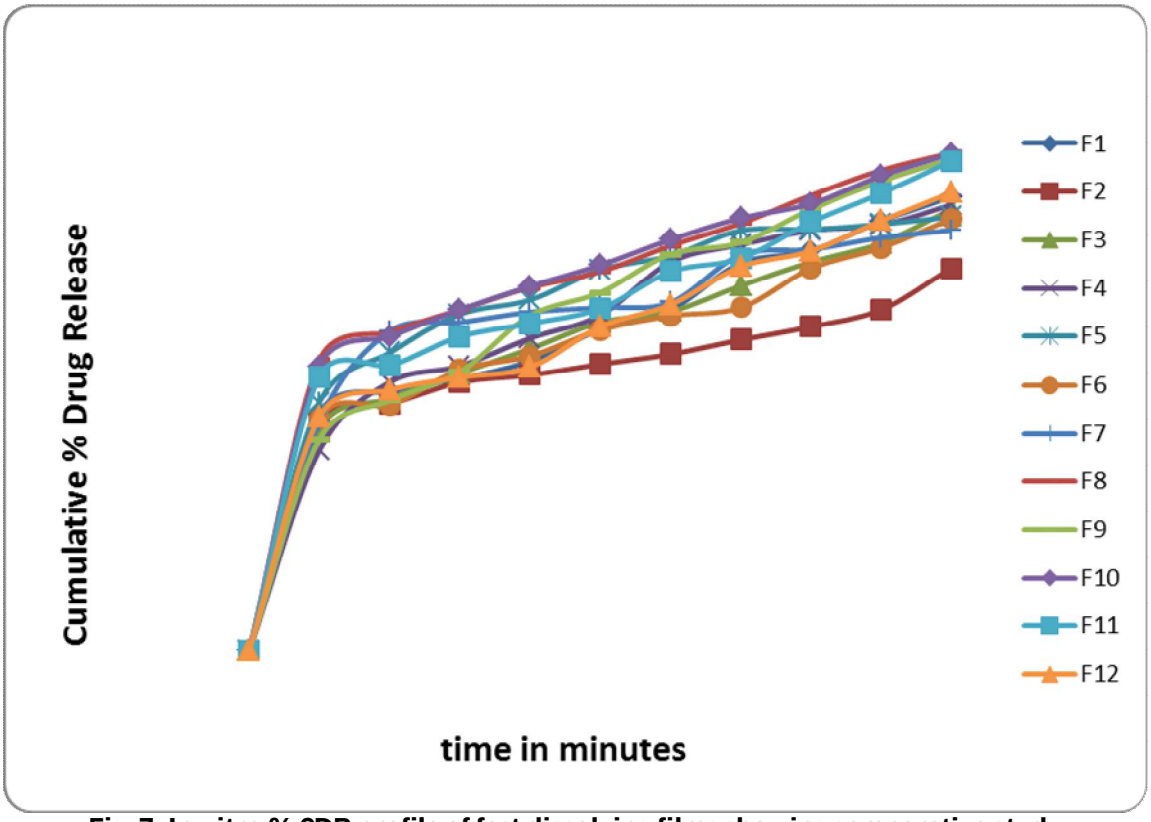

Fig. 7: In-vitro % CDR profile of fast dissolving films showing comparative study

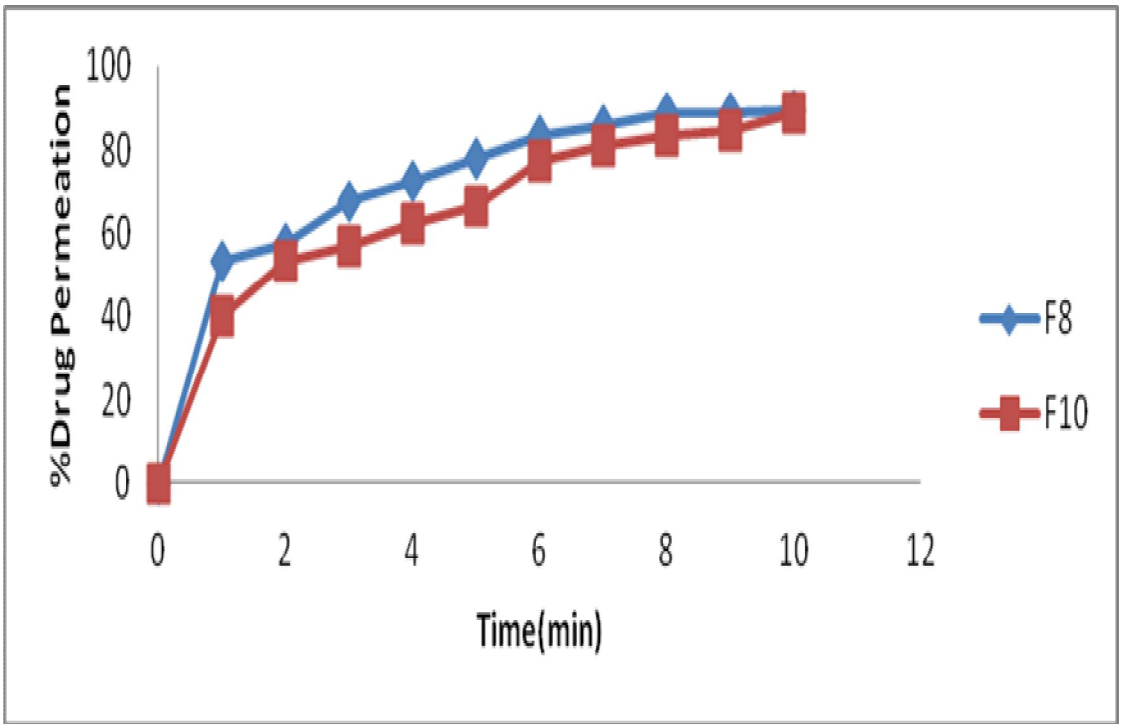

Fig. 8: Ex-vivo Permeation Study of Formulation F8 and F10

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