Research Article

Formulation and Evaluation of Fast Dissolving Buccal Films Containing Zolmitriptan

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ABSTRACT

Fast dissolving oral films are useful in patients such as paediatric, geriatric, bedridden or developmentally disabled who face difficulty in swallowing conventional tablets or capsules and liquid orals or syrups leading to ineffective therapy. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. The present study was aimed to formulate fast dissolving oral films to enhance bioavailability and avoid pre systemic metabolism. The key is to develop successful oral film by solvent casting method and selected the right compatible excipients using FTIR studies. Oral film was fabricated using HPMC-E5, HPM E15, and HPMC- E50 and Propylene glycol.The prepared films were evaluated for Organoleptic evaluations, film weight, thickness, folding endurance, tensile strength, drug content uniformity of films, surface pH, disintegration time and in-vitro dissolution studies. The formulation F5 has disintegration time of 56 seconds and is more promising and showed drug release of 99.89%; hence formulation F5 was selected as best formulation.

Keywords: Oral Films, Metoprolol Succinate, Solvent Casting Method.

INTRODUCTION

Fast-dissolving drug-delivery systems came into existence in the late 1970's as an alternative to tablets, capsules and syrups for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. These systems consist of the solid dosage forms that disintegrate and dissolve quickly in the oral cavity without the administration of water. Research and development in the oral drug delivery segment has led to transition of dosage forms from simple conventional tablets or capsules to modified release tablets or capsules to oral disintegrating tablet (ODT) to wafer to the recent development of oral fast dissolving films (OFDFs). Amongst the plethora of avenues explored for the rapid drug releasing products, oral strip technology is gaining much attention.[1]

Fast dissolving films (FDF), a type of oral drug delivery system for the oral delivery of the drug, was developed based on the technology of the transdermal patch. This delivery system consists of a thin film, which is simply placed on the patient's tongue or mucosal tissue, instantly wet by saliva; the film rapidly dissolves**.** Then it rapidly disintegrates and dissolves to release the medication for oral mucosal absorption.[2]

FDOFs are useful in patients such as pediatric, geriatrics, bedridden, emetic patients, diarrhoea, sudden episode of allergic attacks, or coughing for those who have an active life style. It is also useful whether local action desired such as local anesthetic for toothaches, oral ulcers, cold sores or teething. The OTFs place as an alternative in the market due to the consumer's preference for a fast-dissolving product over conventional tablets / capsules. The oral thin-film technology is still in the beginning stages and has bright future ahead because it fulfils all the need of patients. Eventually, film formulations having drug/s will be commercially launched using the OTF technology.[3]

Metoprolol succinate is β1 selective (cardioselective) adrinoceptaor blocking agent. It is used as anti-hypertensive, anti-anginal and in acute myocardial infarction. The bioavailability of the Metoprolol succinate is about 40-50%, with 3-4 hr half life. In hypertention,it is given in 50

mg daily and according to response the dose may increases to 400 mg[4].

MATERIAL AND METHOD

Zolmitriptan was obtained as gift sample from Gift sample from Celon labs, Hyderabad,. HPMC E-5, MOLY CHEM, Mumbai, India. And HPMC E-15 was obtained as a gift sample from LOBA CHEME pvt.ltd, Mumbai, India. HPMC E-50 was obtained as a gift sample from Rolex Chemical Industries, Bombay . Propylene glycol was obtained as a gift sample from Kemphasol, Bombay**.** Sodium saccharine was obtained as a gift sample from Sd fiN-CHEM limited, Mumbai. Citric acid Fine was obtained as a gift sample from CHEM INDUSTRIES, Chennai.

Preparation of Fast Dissolving Oral Films[5]

Calculation of drug loaded in the film

Diameter of Petridish

Total area of petri dish = 64 cm^2
Each film area = 2×2 = 4 cm2
Number of films in batch =64/6 =10.66
Approximately 12 films

Procedure

The mouth dissolving films of Zolmitriptan were formulated by solvent casting method, by dissolving weighed quantity of drug in required volume of water

The selected concentration of polymers were added to another beaker and dissolve by adding sufficient amount of water. Then both the solutions were mixed together. Initially stirring was carried out at low RPM and later at higher speed. The required quantity of plasticizer was added drop wise. The solution was casted on to Petri dish (area of 64 cm^2) within inverted funnel and allowing to dry overnight at room temperature. The film were removed carefully and an area of 4 cm^2 was punched out so that each film contained 2.5mg of the drug. The dried film were wrapped in butter paper then covered with aluminum foil and kept in desiccators.

Each film with surface area of approximately 4 cm^2 as seen in figure 1 & 2. Each film was loaded with 40mg of Zolmitriptan and each strip contains 2.5mg of drug.

EVALUATION OF FAST DISSOLVING ORAL FILMS

Organoleptic Evaluations

Formulated films were evaluated for oraganoleptic evaluations like Color, odor and taste.

Physical Appearance and Surface Texture

Physical appearance was checked by visual inspection and surface texture was evaluated by touch or feel of the film.

Weight Uniformity[6]

2 × 2 cm^2 film was cut at three different places in the cast film. The weight of each film was checked with the help of an electronic balance and the average weight was calculated.

Fig. 1: The prepared oral strips

Fig. 2: The prepared oral film

Folding Endurance[6]
Folding endurance was determined by repeatedly folding the film at the same position until it breaks. The number of times the films can be folded without breaking is termed as the folding endurance value.

Tensile Strength[7]
Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. The film size 5 x 2 cm2 and free of physical imperfection was placed between two clamps held 10mm apart. The film was pulled by clamp at a rate of 5mm/min.
It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below:
This test was done on randomly selected three films from each batch and average values were reported.

Percentage Elongation[7]
When stress is applied, a film sample stretches, and this is referred to as a strain. Strain is basically the deformation of film divided by the original dimension of the sample.

Thickness of Films[7]
The thickness of three randomly selected films from every batch was determined using a standard Vernier Caliper and average values were reported.

Disintegration Time[8]
It can be performed by two methods for oral films

Slide frame method: one drop of distilled water was dropped by a Pipette onto the oral films. Therefore the films were clamped into slide frames and were placed planar on a Petri dish. The time until the film dissolved and caused a hole within the film was measured.
Petridish method: 2 mL of distilled water was placed in a Petridish and one film was added on the surface of the water and the time measured until the oral film was dissolved completely.
This test was done on randomly selected three films from each batch and average values were reported.

Surface pH[9]
The surface pH of the films was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined glass electrode was used for this purpose. The 2 cm X 2 cm film was dissolved in 2 ml of distilled water. The pH was measured by bringing the electrode in contact with the surface of the film and allowing it to equilibrate for 1 minute. The experiments were performed in triplicate and average values were reported.

Drug Content of Films (% Assay)[10]
Standard preparatio
Weighed accurately 5 mg of Metoprolol Succinate was dissolved in100 mL pH 6.8 phosphate buffer. Diluted 1mL of this solution to 10mL with pH 6.8 phosphate buffer.

Test Preparation
A sample film of size 2×2cm2 which were placed in a beaker containing 100 ml of methanol. Diluted 10 mL of this solution to 10 mL with methanol.

Procedure
Absorbance of standard preparation and test preparation was taken using UV double beam spectrophotometer at 222 nm and % assay was calculated.

***In-Vitro* Drug Release**[11]
The *in vitro* dissolution study is carried out in stimulated saliva solution pH 6.8 phosphate buffer using USP paddle (Type II) apparatus at 37±0.5°C. Samples are withdrawn at regular time interval and analyzed by UV-Visible spectrophotometer. By this method cumulativedrug release and cumulative percentage of drug retained were calculated. *In-vitro* drug dissolution was performed using USP paddle apparatus. The studies were carried out at 37°C with stirring speed of 75 rpm in 900 mL of pH 6.8 phosphate buffer dissolution medium. 5 ml of samples were withdrawn at predetermined time intervals of 2, 4, 6, 8, 10 minutes and replaced with the same volume of buffer. The samples were collected and the absorbance was determined at 222 nm UV-visible spectrophotometer.
The results of *in-vitro* release data obtained for all formulations were fitted in two popular models of data treatments as follows:
i. Zero-order kinetic model (cumulative percent drug released versus time)
ii. First-order kinetic model (log cumulative percent drug remaining versus time).

RESULT AND DISCUSSION

FTIR studies: FTIR studies were performed to detect the possible molecular interaction between drug (Zolmitriptan) and utilized polymers (HPMC E-5, HPMC E-15, HPMC E-50, Propylene glycol). FTIR spectra were showned in *Figures* and spectral data was depicted in *Table* . The comparision between FTIR spectrum of physical mixture of drug with excipients and pure Zolmitriptan revealed that there was no appreciable change in position and intensity of peak with respect to IR spectrum of pure Zolmitriptan, indicates there was no interaction between drug and utilized polymers.

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EVALUATION OF FAST DISSOLVING FILMS

Nine formulations F1 to F9 of fast dissolving buccal films containing Zimitriptan. solid dispersion were prepared by solvent casting method using HPMC E-5,HPMC E-15,HPMC E-50 as a film forming polymer and Pr as a propylene glycol plasticizer. All the prepared fast dissolving buccal films were evaluated for their physiochemical parameters like thickness & weight of the films, surface pH, Swelling index, PMA, folding endurance, disintegration time, drug content and *invitro* release studies.

Visual inspection

All the films prepared were found to be flexible, smooth, non sticky, homogenous, yellow colored and transparent with no visible particulate matter

Thickness measurements

Thickness of mouth dissolving film depends on the concentration of polymer. Thickness of all mouth dissolving films was measured with micrometer screw gauge. The thickness was found to vary between 0.1 to 0.2 mm with very low standard deviation value . A very low standard deviation value indicating that the method used for the formulation of films gives films of uniform thickness and hence dosage accuracy in each film can be ensured. The results indicating that as the concentration of polymer increases, thickness of fast dissolving film increases.

Weight variation

The observed results of Weight variation test were showed in *Table* . The results revealed that the weight of the films varied with polymer concentration. Increase in polymer concentration resulted in increase in weight of the film, but the increase was marginal

Folding endurance

Folding endurance gives an indication about brittleness of the film. The folding endurance of the prepared films was found to be ranged from 48 to 101 percent. Among all the formulations, F6 formulation which contain higher concentration i.e.20% of plasticizer (propylene glycol) has shown higher folding endurance of 76.3%. From the results it was concluded that as the concentration of plasticizer increases, folding endurance of fast dissolving film increase

Surface pH study

The surface pH of the films was found between 6.5-6.7. The surface pH of all the formulations were close to the neutral pH, which indicated that films may have less potential to irritate the buccal mucosa, and hence, more acceptable by the patients

Disintegration time

It was observed that *in-vitro* disintegration time varies from 44-56 sec. *In-vitro* disintegration time of the films was found to be increased with increasing the concentration of the polymer, because high concentration of polymer resulted in a thicker gel upon contact with the medium, resulting in longer disintegration time. It was also found that there was no significant increase in the disintegration time on increasing the concentration of Propylene glycol (plasticizer) from 7.5% to 20%. Overall the disintegration time of all formulations were found to minimum as compared to other dosage forms, which is desirable for faster absorption and rapid onset of action

Drug uniformity

Drug content in the films were found to be between 95.71 to 100.29 %. As per USP requirements, the films found to meet the criteria for content uniformity 85- 115 % of the label claim. It was observed that no significant difference in the drug content among all the films which indicates, the drug was dispersed uniformly throughout the 6 cm^2 constant area of the film.

The formulated films were subjected for *invitro* dissolution studies and the results were shown in Table 6.15. Among the six formulations prepared, formulation F5 was found to release 99.89% drug with in 7 min which is desirable for faster absorption and rapid onset of action The release kinetics of all formulations can be explained by comparing the correlation coefficients values for their Zero order and First

order regression equations. The correlation coefficient values for the release profiles of the Zolmitriptan film formulations in Phosphate buffer of pH 6.8 were given in *Table 12*. The data has shown that correlation coefficient (R^2) values for First order plots regression values were higher than that of Zero order regression equations. Thus the Zolmitriptan film formulations were found to follow first order release kinetics.

CONCLUSIONS

Pre formulation study involving FTIR study showed no interaction between drug and polymer. Fast dissolving films prepared in the study exhibited good film characteristic features as indicated by thickness measured, folding endurance, disintegration time, tensile strength and drug content. Overall, these findings indicate that fast dissolving buccal films of Zolmitriptan was the most suitable dosage form for clinical use in the treatment of migrane, where a quicker onset of action for a dosage form is desirable along with the improved bioavailability and convenience of administration.

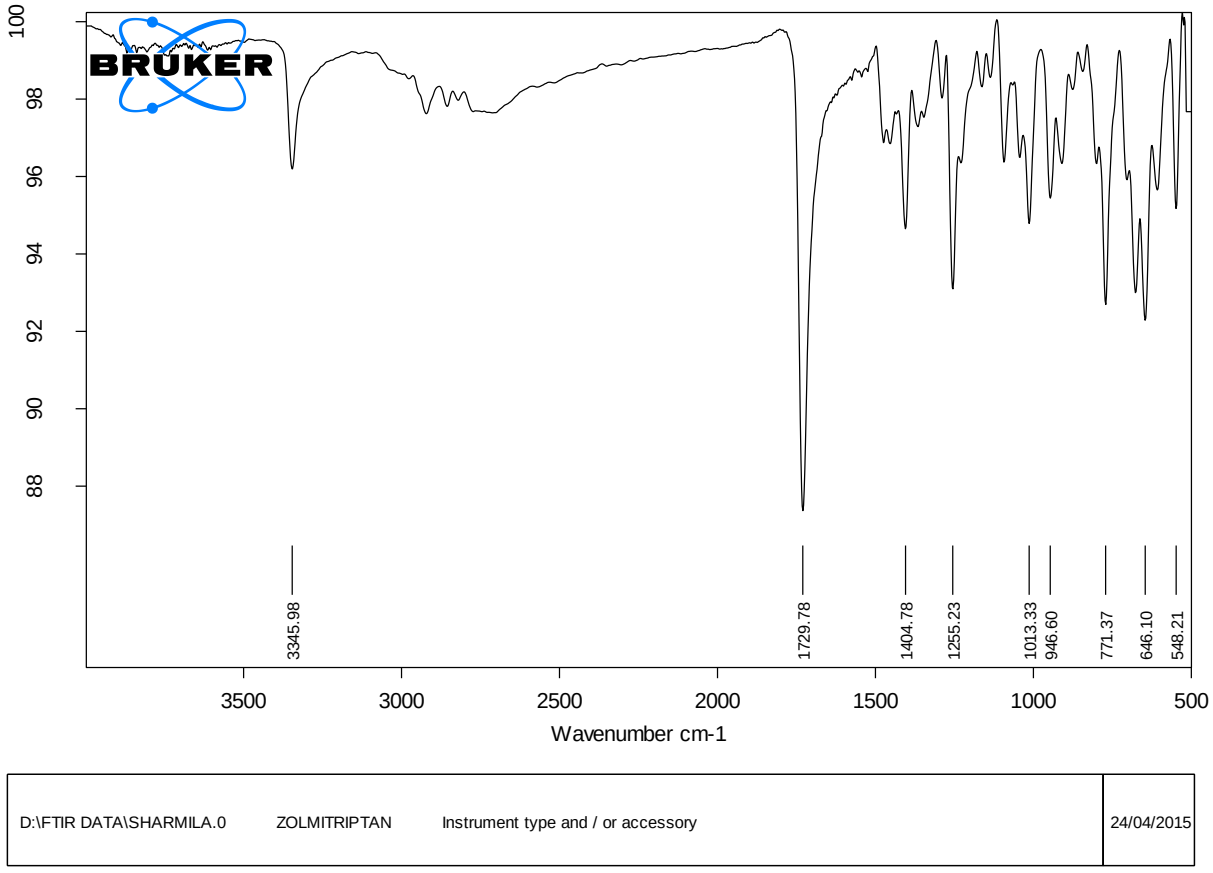


Fig. 3: **FT-IR spectrum of pure Zolmitriptan**

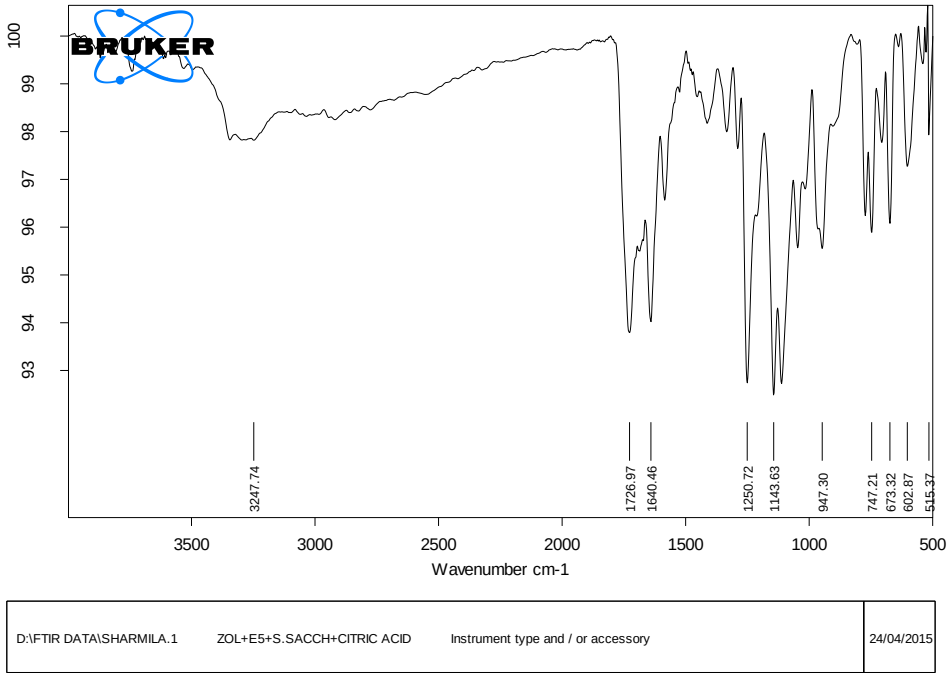


Fig. 4: **FT-IR spectrum of HPMC E-5**

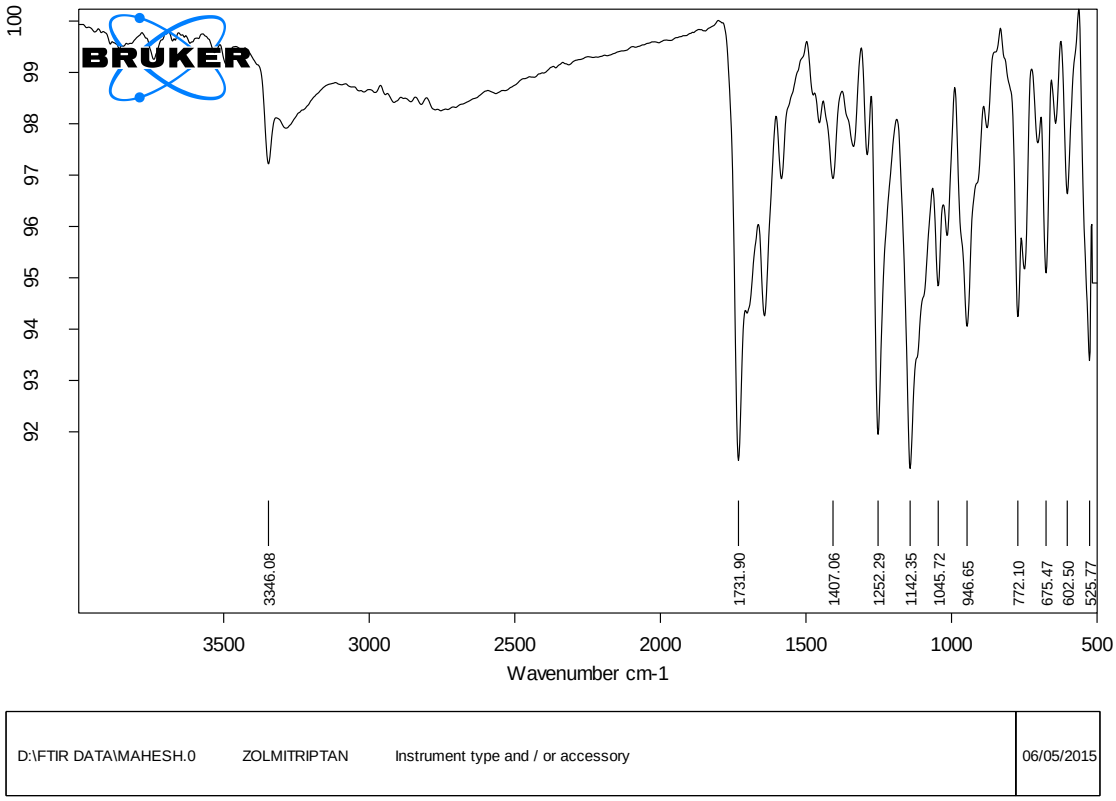


Fig. 5: FT-IR spectrum of HPMC E-15

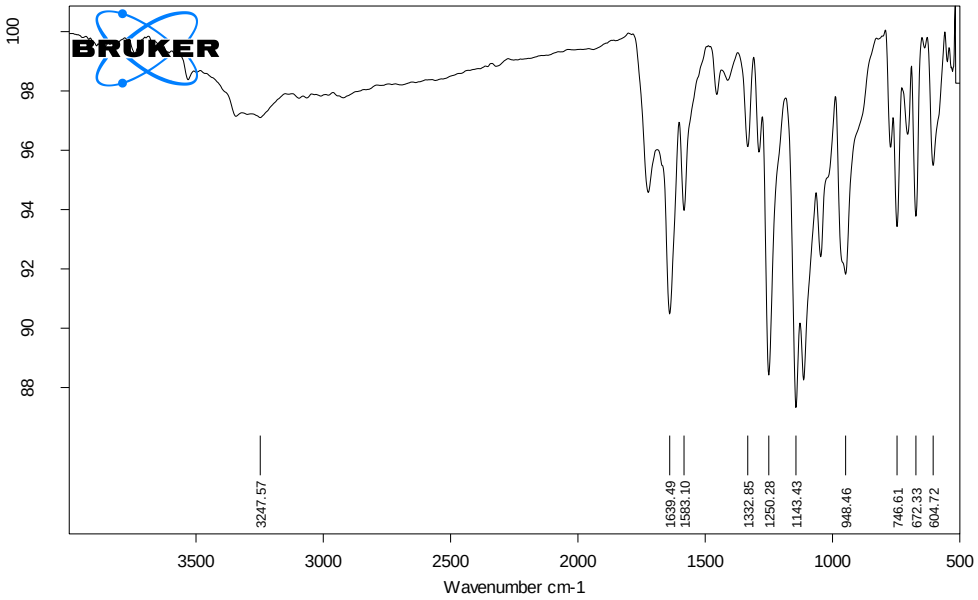


Fig. 6: **FT-IR spectrum of HPMC E-50**

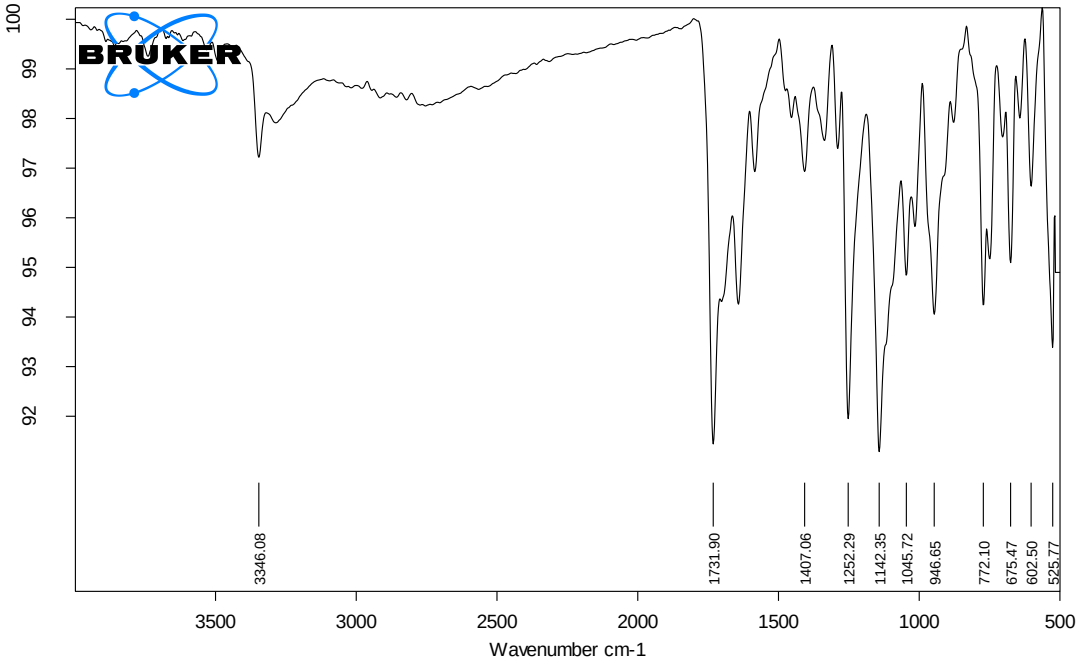


Fig. 7: HPMC E-15 Optimized film (f5)

Table 1: Composition of Zolmitriptan Buccal Films

Ingredients(mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Zolmitriptan	40	40	40	40	40	40	40	40	40
HPMC-E_5	200	300	400						
HPMC-E_{15}				200	300	400			
HPMC-E_{50}							200	300	400
Propylene glycol(%w/w)	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.14
Citric acid	1	1	1	1	1	1	1	1	1
Sodium saccharin	1	1	1	1	1	1	1	1	1
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table 2: Physical Characterization Of Fast Dissolving Oral Films

FORMULATION CODE	Thickness of the film	Weight of the film in mg	Folding endurance of the film (%)	Surface pH of the film	Disintegration time(sec	PMA of the film (%)
F1	0.1±0.01	10±0.1	48.3±0.01	6.50±0.09	44.3±3.35	96.70±2.47
F2	0.1±0.01	10.6±0.15	50.6±0.015	6.74±0.03	46±2.32	99.28±5.90
F3	0.1±0.01	12.3±0.2	54.3±0.02	6.56±0.12	46.6±2.32	100.29±2.20
F4	0.2±0.02	11.5±0.16	56±0.025	6.60±0.04	48.3±2.33	96.51±3.80
F5	0.2±0.02	12.3±0.2	82±0.04	6.73±0.04	56±1.01	97.22±3.90
F6	0.2±0.02	12.3±0.2	83±0.045	6.69±0.03	50±0.98	99.71±1.36
F7	0.25±0.02	12.5±0.25	91.6±0.05	6.80±0.03	51.6±1.00	96.51±3.80
F8	0.25±0.02	12.7±0.26	97.6±0.15	6.60±0.04	55±1.00	95.24±2.46
F9	0.25±0.02	13±0.3	100.3±0.16	6.74±0.03	56±1.00	95.18±2.44

Table 3: In-vitro drug release studies of E_5

TIME (mins)	% of drug dissolved		
	F1	F2	F3
1	89	87.9	82
2	92	91.2	88.2
4	97	96	93
6	99.5	99.6	97
8	-	-	99.4
10	-	-	
12	-	-	

Table 4: In –vitro drug release studies of E_{15}

TIME (mins)	% of drug dissolved		
	F4	F5	F6
1	84	78	72
2	87.9	80	79
4	91	86.3	82
6	95	90.4	85
8	98.9	94.8	91
10	-	98.5	95
12	-	99.2	98.5

Table 5: In-vitro drug release studies of E_{50}

TIME (mins)	% of drug dissolved		
	F7	F8	F9
1	68	64	59.8
2	71	69	63.5
4	76	74.7	68.4
6	78.9	76.4	71.2
8	84	79.8	74.5
10	88	81.36	77.5
12	91	84.4	80.4

Table 6: Correlation coefficient values of R^2

Formulation code	Correlation coefficient (R^2) values of various release kinetics	
	Zero order	First order
F1	0.9841	0.9205
F2	0.9852	0.9205
F3	0.9742	0.9292
F4	0.4428	0.8694
F5	0.4741	0.9356
F6	0.5069	0.8951
F7	0.5085	0.8265
F8	0.4675	0.7026
F9	0.4992	0.7177

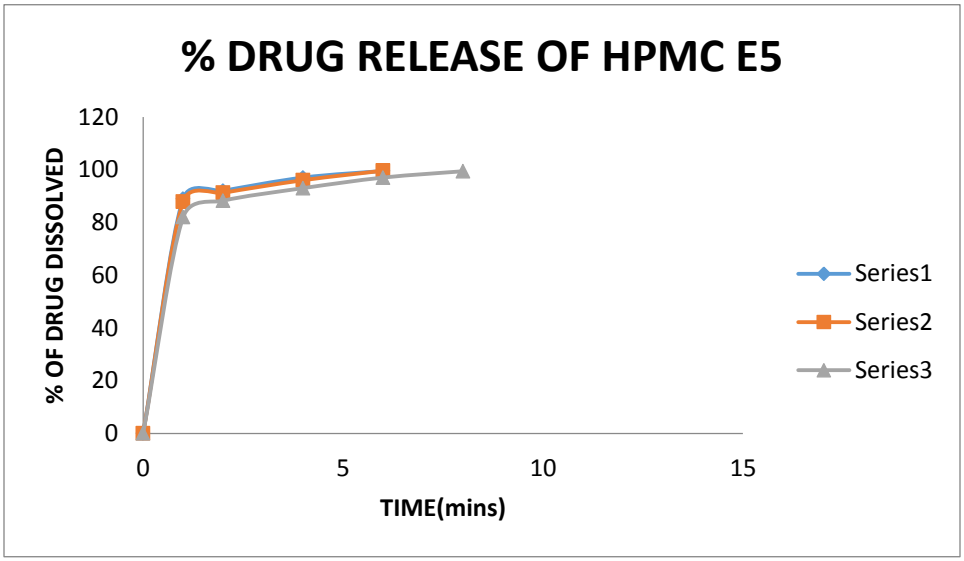
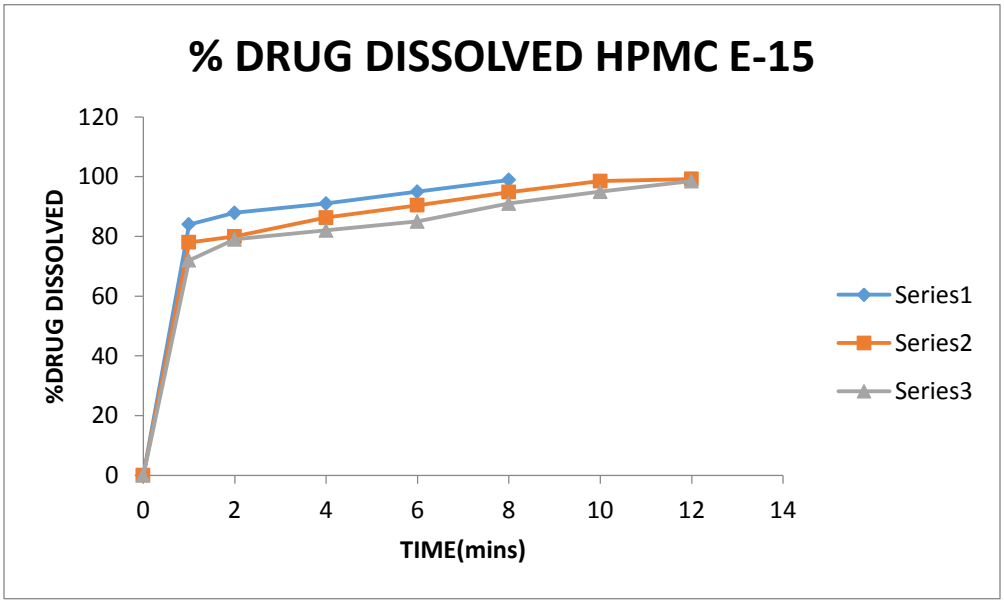


Fig. 8



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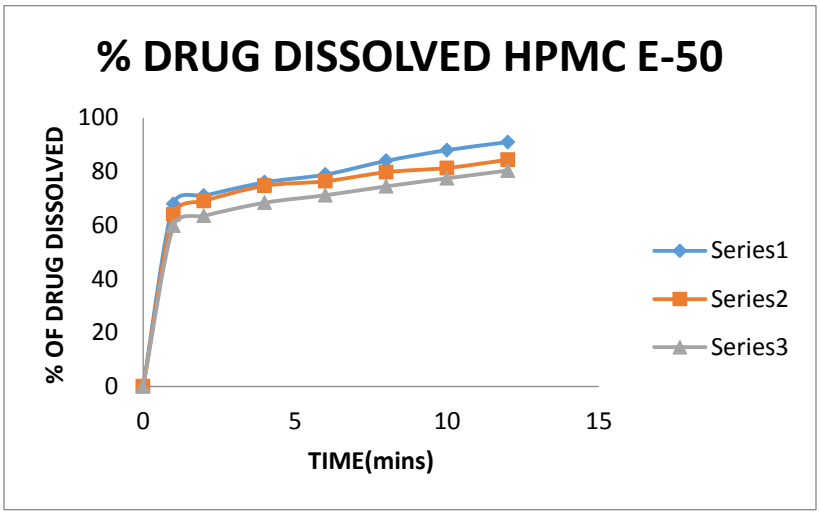

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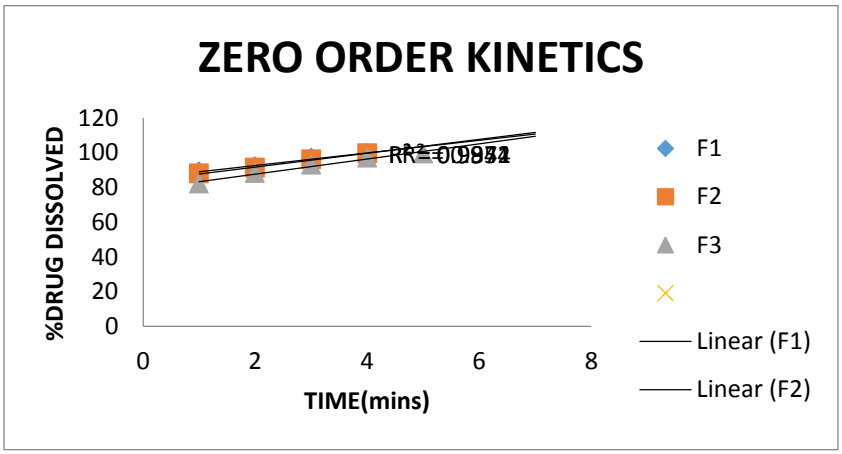

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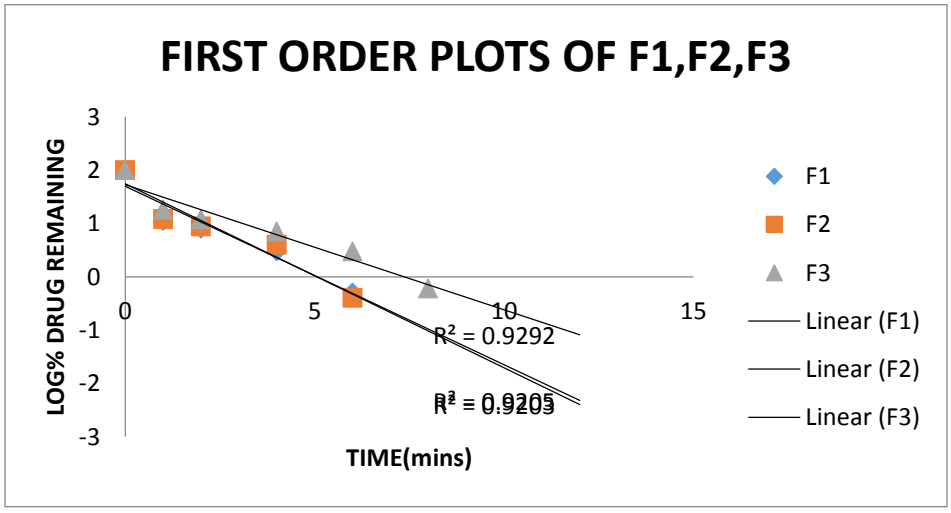
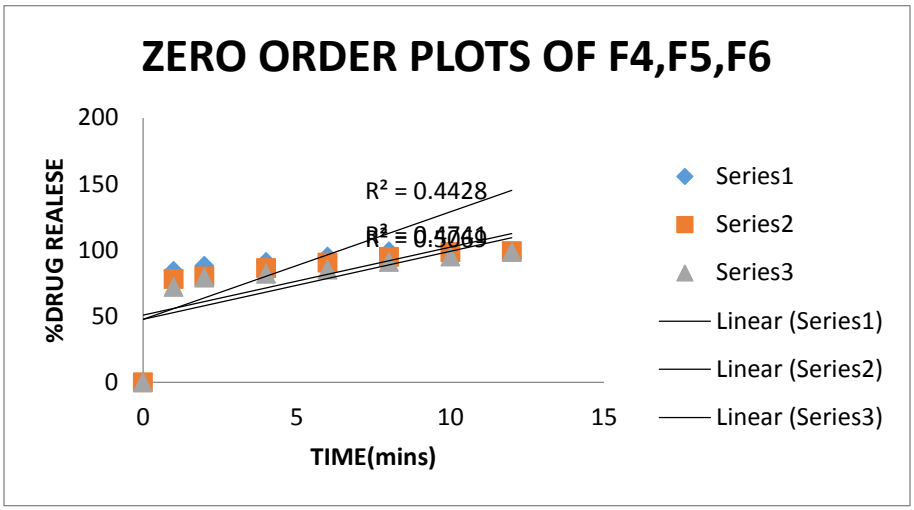


Fig. 12



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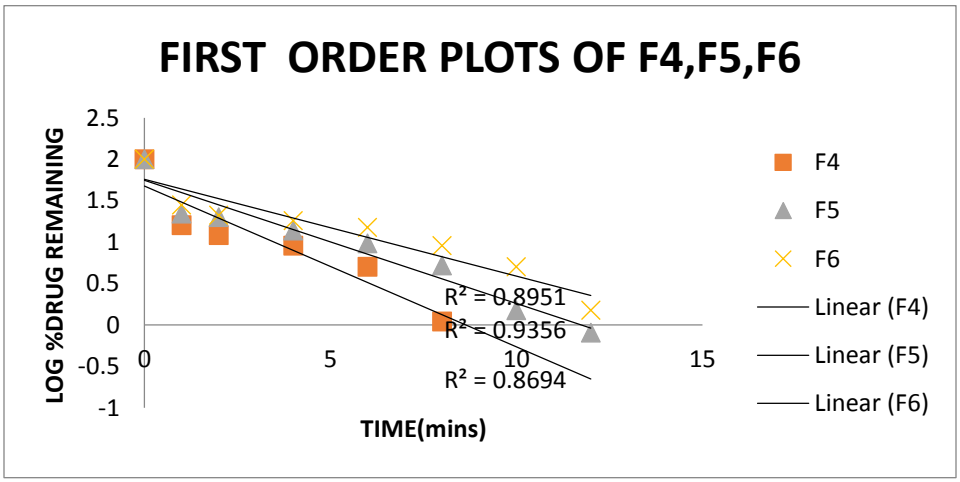

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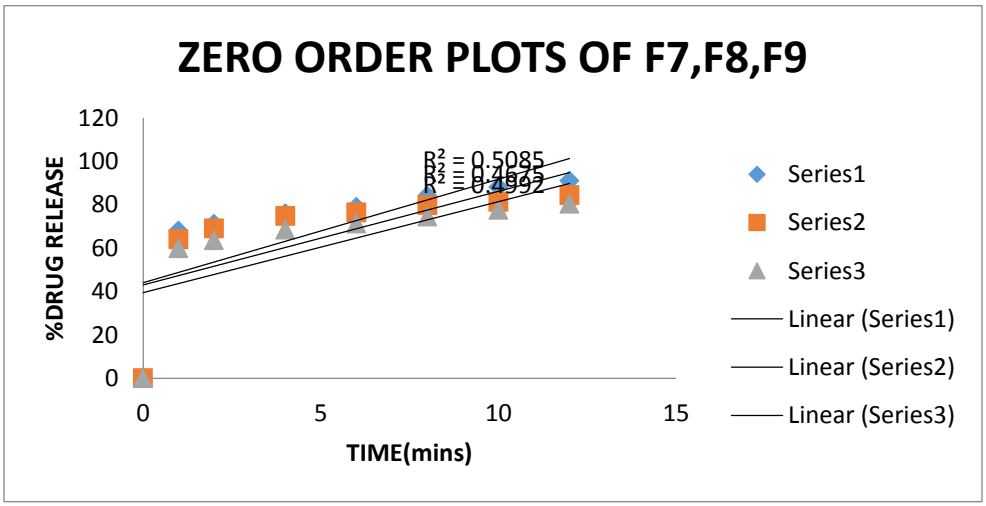

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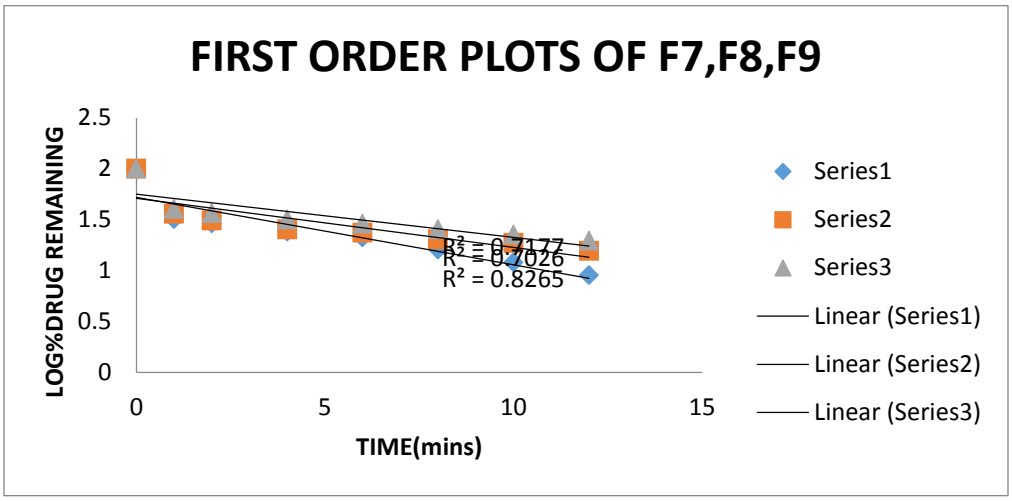

Fig. 16

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