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Original Article

Formulation and Evaluation of Fast Dissolving Oral Films of Zolmitriptan

A. Deepthi*, B. Venkateswara Reddy, and K. Navaneetha

Department of pharmaceutics, St. Pauls College of Pharmacy, Turkayamjal (V), Hayathnagar (M), Ranga Reddy Dist-501510, A.P. India.

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Address for Correspondence
Department of pharmaceutics, St. Pauls College of Pharmacy, Turkayamjal (V), Hayathnagar (M), Ranga Reddy Dist-501510, A.P. India.

Tel. +91-9550657064.
E-mail: deepthireddyananthula@gmail.com

ABSTRACT

The present study was aimed to formulate and evaluate fast dissolving oral films of Zolmitriptan using sodium alginate, xanthan gum and sodium starch glycolate, guar gum. The suitable plasticizer and its concentration were selected on the basis of flexibility, tensile strength and stickiness of the film. The films are prepared by solvent casting method and characterized by UV, FTIR studies. The films were evaluated for disintegration time, Folding endurance, Tensile Strength, Mouth dissolving time, Thickness, content uniformity and *In-vitro* dissolution studies. The F_5 formulation has given 98.5% drug release within 6 minutes and has a tensile strength of 1.80 MPa.

Keywords: Zolmitriptan, Sodium alginate, Aloevera and Solvent casting.

INTRODUCTION

Fast dissolving oral films (FDOFs) or Oral wafers or Oral strips (OS) or sublingual strips or oral thin films (OTF) are the most advanced form of oral solid dosage form due to more flexibility and comfort[1]. It improves the efficacy of APIs by dissolving within minute in oral cavity after the contact with saliva without chewing and no need of water for administration. It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa is 4-1000 times greater than that of skin[2,3]. FDOFs are useful in patients such as pediatric, geriatrics, bedridden, emetic patients, diarrhea, sudden episode of allergic attacks, or coughing for those who have an active life style[4,5]. It is also useful whether local action desired such as local anesthetic for toothaches, oral ulcers, cold sores or teething. At present Zolmitriptan is available in the form of tablets, nasal sprays in the market. Patients

are non co-operative with these dosage forms[6]. Hence oral disintegrating films have become important tool to improve the patient compliance.

MATERIALS AND METHODS

Chemicals

Zolmitriptan was obtained from Chandra labs, Hyderabad, India. Remaining other chemicals like Guar gum, Xanthan gum, Alovera, Sodium alginate, Poly ethylene glycol 400, Sodium starch glycolate, Vanillin, Sodium Saccharine were obtained from Research-lab fine Chem industries Mumbai.

Preparation of fast dissolving oral films[7,8]

Film was prepared by using specified polymer by solvent casting method. The specified amount of polymer was weighed and dissolved in specified amount of water for overnight to get a uniform dispersion of different % (w/v) solutions. Drug, sodium starch glycolate, vanillin were dissolved in specific amount of water in a beaker. The drug solution was added to the polymer solution and mixed using magnetic stirrer for 1 hour. The resulting solution was degassed so as to remove any bubbles formed. The bubble free solution was casted on to a Petri dish of surface area 28.26 cm^2. It was dried for 24 hours at room temperature. The film was removed from the Petri dish very carefully and observed for any imperfections. Film that was clear and bubble free was selected for further studies. Film of area 2.25 cm^2 (1.25 X 1.25) was cut and stored in a butter paper covered with aluminum foil and stored in desiccators. Composition of various formulations is shown in table-1 and the images of the films are given in the figures 1, 2, 3 and 4.

Drug polymer compatibility studies

Study was carried out using FT-IR spectrometer. FT-IR Spectra of Zolmitriptan and polymers with Zolmitriptan were obtained. The spectrum was studied for specific peaks of drug and polymer. The spectra are shown in figure 5-9.

Physical characterization of fast dissolving oral films[9,10]

A. Weight variation of the film

2.25 cm^2 films were cut at five different places in the caste film. The weight of each filmstrip was taken and the weight variation was calculated.

B. Thickness of the film

The thickness of the patch was measured using digital Vernier Calipers with a least count of 0.01 mm at different spots of the film. The thickness was measured at three different spots of the patch and average was taken and SD was calculated.

C. Tensile strength

Tensile testing was conducted using a texture analyzer AG/MC1 (Acquati, Italy), equipped with a 5 N load cell. The film was cut into 30 × 20 mm strips. Tensile tests were performed according to ASTM International Test Method for Thin Plastic Sheeting (D 882-02). Each test strip was placed in tensile grips on the texture analyzer. Initial grip separation was 20 mm and crosshead speed was 1 inch/min. The test was considered concluded when the film breaks. Tensile strength, was computed with help of load require to break the film and cross sectional area to evaluate tensile properties of the films. Tensile strength (TS) Tensile strength is the maximum stress applied to a point at which the film specimen breaks and can be calculated by dividing the maximum load by the original cross-sectional area of the specimen and it was expressed in force per unit area (MPa).

Tensile Strength = Force at break (N)/ Cross sectional area (mm^2)

D. Folding endurance

The folding endurance is expressed as the number of folds (number of times of film is folded at the same plain) required breaking the specimen or developing visible cracks. This gives an indication of brittleness of the film. A small strip of 4 square cm was subjected to this test by folding the film at the same plane repeatedly several times until a visible crack was observed.

E. Disintegration time

Test was performed using disintegration test apparatus. 2.25 cm2 film was placed in the basket, raised and lowered it in such a manner that the complete up and down movement at a rate equivalent to thirty times a minute. Time required by the film, when no traces of film remain above the gauze was noted.

F. Mouth dissolving time

The mouth dissolving time was determined by placing the film manually into a beaker containing 50 ml of 7.4 pH phosphate buffer. Time required by the film to dissolve was noted.

G. Content uniformity

The films were tested for content uniformity. Films of 2.25 cm2 was cut, placed in 100 ml volumetric flask and dissolved in methanol, volume was made up to 100 ml with methanol. Solution was suitably diluted. The absorbance of the solution was measured at 228 nm.

H. *In vitro* Dissolution studies

Dissolution study was carried out using USP type I (basket apparatus) with 300 ml of pH 7.4 Phosphate buffer as dissolution medium maintained at 37 ± 0.5^{O}C. Medium was stirred at 50 rpm for a period of 30 minutes. Samples were withdrawn at every 1 min interval up to 30 min, replacing the same amount with the fresh medium. Samples were suitable diluted with pH 7.4 and analyzed for drug content at 228 nm.

I. Stability studies[11]

The optimized batch F5 was packed in a butter paper covered with aluminum foil and was isothermally stressed to study the stability under accelerated temperature and relative humidity conditions carried out at 40°C/75% RH, 25°C/60% RH and 25°C/40% RH for a period of 3 months. Test samples were withdrawn every month and were subjected to various tests including visual inspection of the film, disintegration time and cumulative percent of drug release. The results are given in Table-4.

RESULTS AND DISCUSSION

Drug polymer compatibility studies

FTIR studies conducted on pure drug and mixture of drug and excipients (Figures 5, 6, 7, 8, and 9) showed that there is no marked interaction between drug and excipients selected. The graphs obtained indicate that the drug is compatible with the excipients used.

Physical characterization of fast dissolving oral films

The physical characterization of the formulated oral films were done by various techniques mentioned and the results were tabulated in Table-2 for various parameters like weight variation of the films, thickness of the films, Tensile strength of the films, Folding endurance of the films, Disintegration time, Mouth dissolving time, Drug content uniformity of films, *In-vitro* dissolution.

Weight variation varies from 41.4 ± 0.43 to 56.16 ± 0.87 mg, as the polymer concentration increases the thickness, folding endurance and disintegration time of the film also increases. The formulation F5 shows 33 Sec (disintegration time). The formulation F_2 shows the maximum value of tensile strength 4.32 ± 0.02 and folding endurance was 181

this might be due to the formation of strong hydrogen bonds between polymer and plasticizer there by imparting flexibility to withstand rupture. The *In-vitro* drug release from the formulation f_5 was 98.5% within 7 mins of time and values are given in table-3. The results of the stability studies are given in the table-4.

CONCLUSIONS

The Zolmitriptan is a serotonin (5-HT1) agonist used for the treatment of migraine with or without aura. The half-life of Zolmitriptan is 2.5 to 3 hrs and it undergoes hepatic metabolism, the absolute oral bioavailability is about 40 to 50%. So, in order to improve the bioavailability and efficacy, we have prepared fast dissolving films of Zolmitriptan.

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, and mouth dissolving time, tensile strength and drug content.

The prepared films were found to be uniform, flexible and 98.5% of drug was released from F_5 film within 6 minutes which was desirable for fast absorption. Later stability studies of this formulation were indicating that there was no degradation of the formulation at high temperature and humidity conditions. It was indicating that this formulation was stable.

From the present investigation it can be concluded that oral thin film formulation can be a potential novel drug dosage form for pediatric, geriatric and also for general population. Hence fast dissolving films of Zolmitriptan were found to be suitable for eliciting better therapeutic effect in the treatment of migraine.

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Figure 1. Fast dissolving oral films of Aloevera 1.5%, Aloevera (2%)

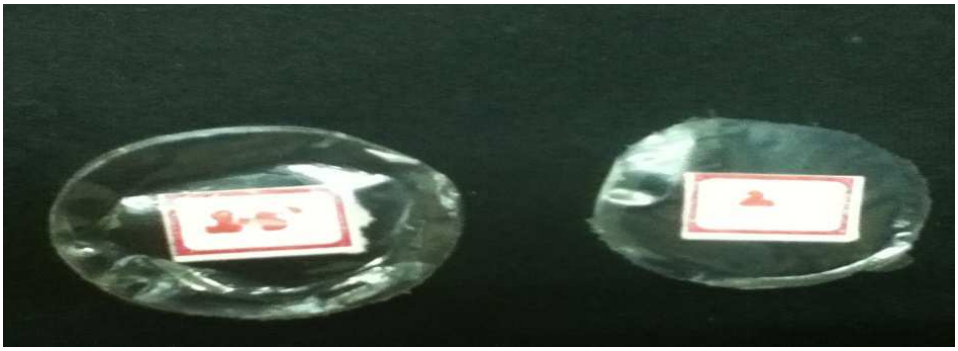

Figure 2. Fast dissolving oral films of sodium alginate 1.5% and 2%

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Figure 3. Fast dissolving oral films of Xanthan gum

Figure 4. Fast dissolving oral films of guar gum

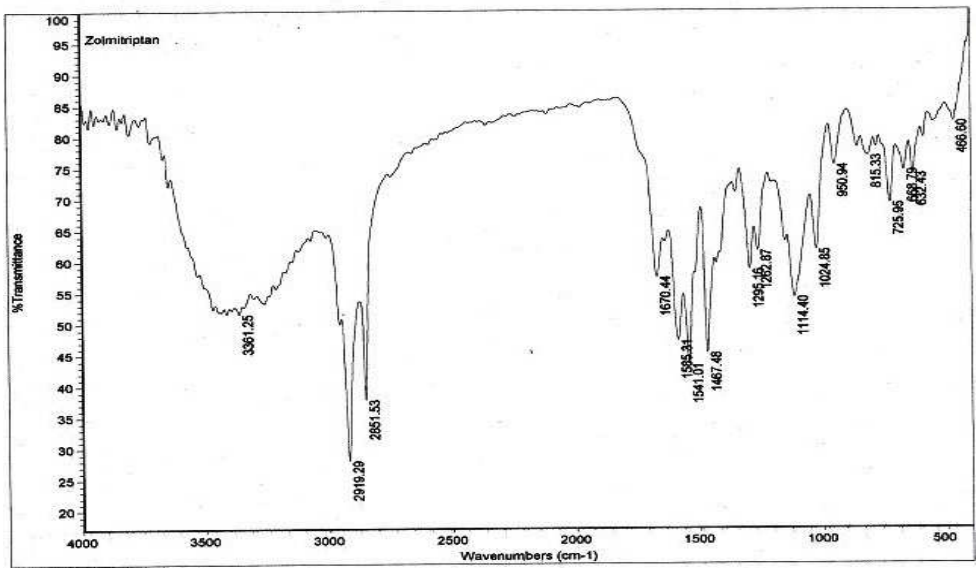

Figure 5. FTIR Studies of Zolmitriptan (Pure Drug)

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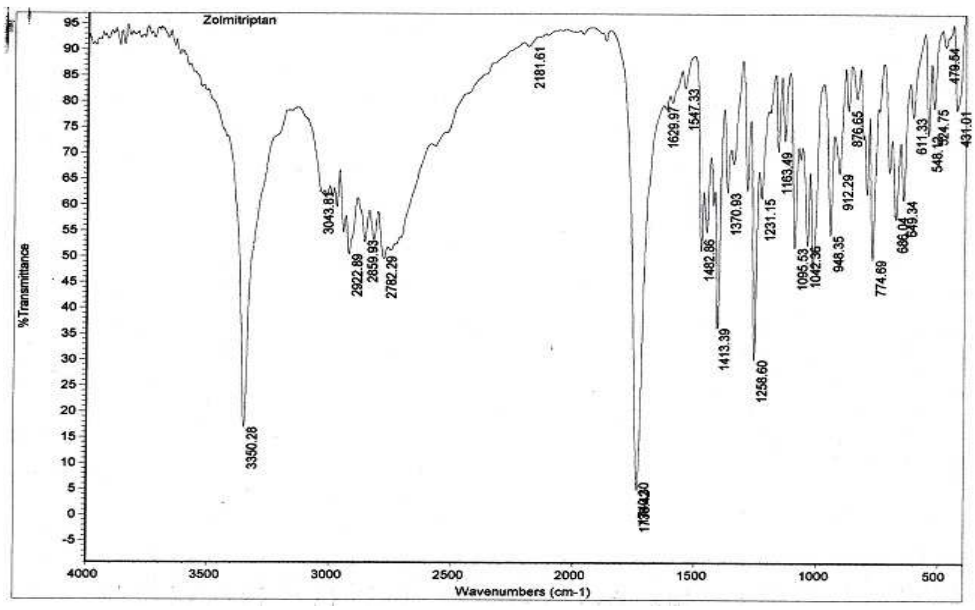

Figure 6. FTIR Studies of Zolmitriptan + Sodium alginate

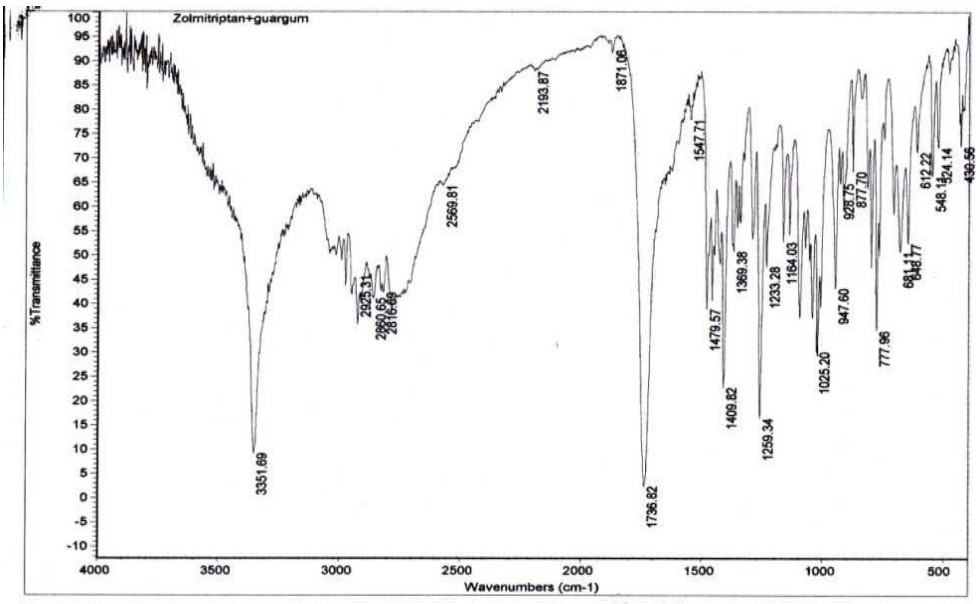

Figure 7. FTIR Studies of Zolmitriptan + Guar gum

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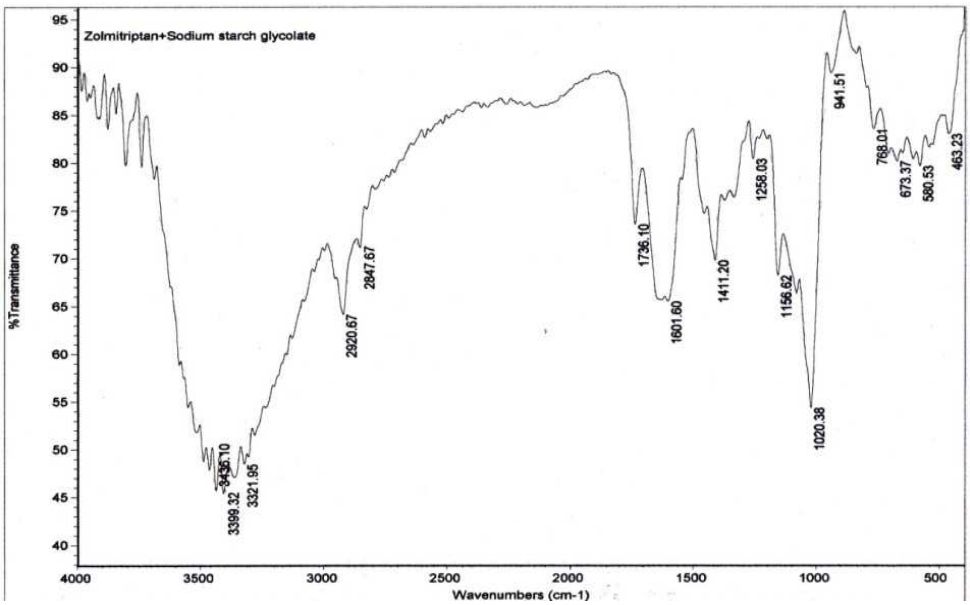

Figure 8. FTIR Studies of Zolmitriptan + Sodium starch glycolate

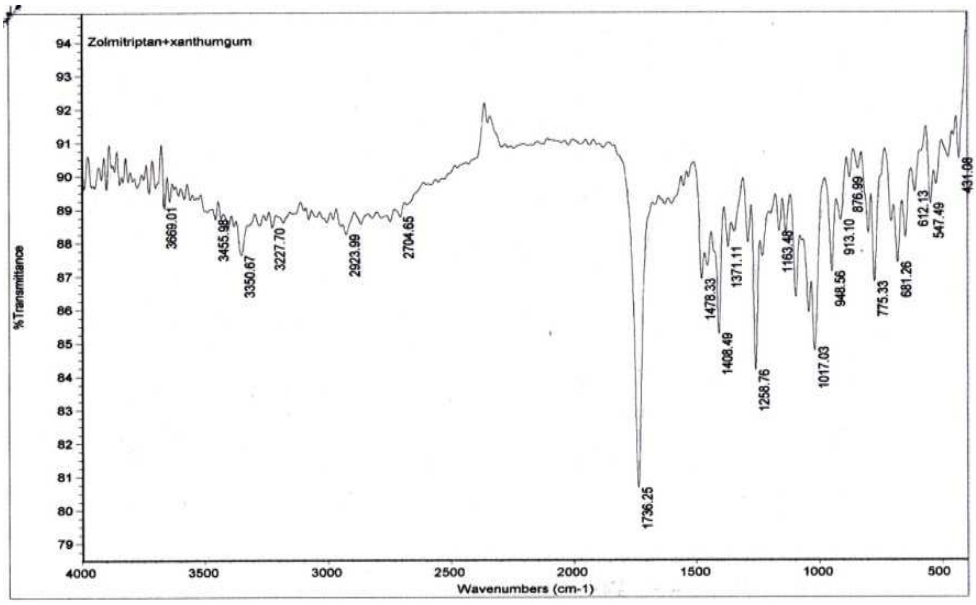

Figure 9. FTIR Studies of Zolmitriptan + Xanthan gum

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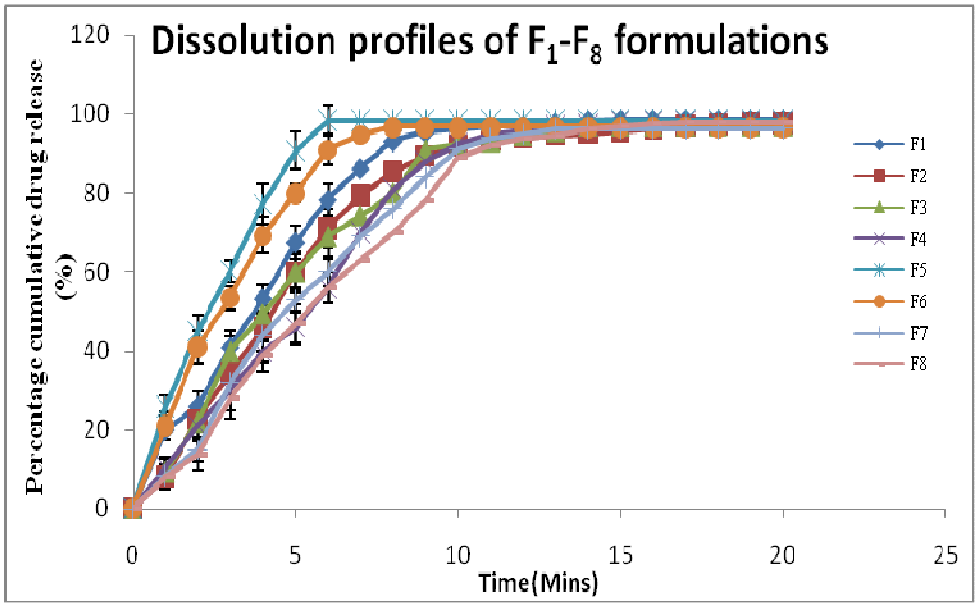

Figure 10. Dissolution profile of fast dissolving oral films

Table 1. Composition of various fast dissolving oral films formulations

S. No	Ingredients (mg/film)	F1	F2	F3	F4	F5	F6	F7	F8
1	Zolmitriptan	5	5	5	5	5	5	5	5
2	Guar gum*	0.4	0.7	-	-	-	-	-	-
3	Xanthan gum*	-	-	0.4	0.7	-	-	-	-
4	Sodium alginate*	-	-	-	-	1.5	2	-	-
5	Aloevera*	-	-	-	-	-	-	1.5	2
6	SSG	2	2	2	2	2	2	2	2
7	PEG 400**	20	20	20	20	20	20	20	20
8	Vanillin	1	1	1	1	1	1	1	1
9	Sodium saccharine	1	1	1	1	1	1	1	1
10	Water	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

*=Expressed as %w/v
** = Expressed as %w/w of the polymer

Table 2. Evaluation of fast dissolving oral films

Formulation code	Weight variation (mg)	Thickness (mm)	Tensile strength (MPa)	Folding endurance (no. of folds)	Disintegration time (sec)	Mouth dissolving time (sec)	Drug content (%)
F_1	42.06 ± 0.51	0.22 ± 0.025	3.83 ± 0.02	160 ± 2.15	46 ± 2	53.6 ± 1.52	99.4 %
F_2	54.75 ± 0.56	0.29 ± 0.01	4.32 ± 0.02	181 ± 3.60	54 ± 2	64.66 ± 3.05	98.2 %
F_3	43.8 ± 0.6	0.18 ± 0.00	3.06 ± 0.06	124 ± 8.14	42 ± 1	47 ± 2	95.6 %
F_4	56.16 ± 0.87	0.23 ± 0.01	3.29 ± 0.01	162 ± 11.01	45.33 ± 1.15	55.33 ± 3.05	95.8 %
F_5	41.4 ± 0.43	0.1 ± 0.02	1.80 ± 0.01	95 ± 6.25	33.33 ± 3.05	40.66 ± 3.04	97.2 %
F_6	52.2 ± 0.65	0.16 ± 0.01	2.12 ± 0.02	110 ± 6.02	46.33 ± 1.52	52.66 ± 3.21	96.8 %
F_7	41.6 ± 0.30	0.21 ± 0.01	2.73 ± 0.02	132 ± 2.08	49 ± 1	59.66 ± 4.04	94.4 %
F_8	52.98 ± 0.41	0.27 ± 0.01	2.97 ± 0.01	156 ± 4.16	57.33 ± 0.57	65.55 ± 2.08	96 %

Table 3. Comparative evaluations of *In-vitro* dissolution profiles of fast dissolving oral films

Time in min	Cumulative % of drug release							
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
1	10 %	8.2%	9.3%	10.6%	26%	21%	8.4%	8%
2	26 %	22.6%	22%	21%	45%	41%	15%	13.6%
3	41 %	34.3%	39.8%	30%	60.3%	53.5%	32%	28%
4	53.3%	45.9%	49.3%	39.8%	77.3%	69.3%	44%	39%
5	67.6%	60%	60%	46%	90.8	80%	53%	47%
6	78.3%	71%	69%	56%	98.5%	90.9%	60%	56%
7	86.3%	79.3%	74.3%	70%	98.5%	94.8%	69%	63%
8	93.2%	85.3%	80%	81%	98.5%	96.8%	76%	70%
9	95.3%	89.3%	90.9%	88%	98.5%	96.8%	84%	78%
10	96.3%	92%	92.4%	92.4%	98.5%	96.8%	91%	89%
11	96.8%	93.1%	93%	95%	98.5%	96.8%	93.8%	92%
12	97.3%	93.9%	94.5%	96%	98.5%	96.8%	94.9%	93.8%
13	97.8%	94.6%	95.6%	96.9%	98.5%	96.8%	96.3%	94.5%
14	98.4%	94.9%	97%	97.3%	98.5%	96.8%	96.3%	96.3%
15	98.6%	95.4%	97%	98%	98.5%	96.8%	96.3%	97%
16	98.6%	96.1%	97%	98%	98.5%	96.8%	96.3%	97.6%
17	98.6%	96.8%	97%	98%	98.5%	96.8%	96.3%	98%
18	98.6%	97.2%	97%	98%	98.5%	96.8%	96.3%	98%
19	98.6%	97.6%	97%	98%	98.5%	96.8%	96.3%	98%
20	98.6%	98	97%	98%	98.5%	96.8%	96.3%	98%

Table 4. Stability Studies

S.NO	Time (Days)	Appearance	*In-vitro* Disintegration Time (Sec)	% CDR
1	Initial (0 Days)	Transparent and Acceptable	33.33 ± 3.05	98.5%
2	1 month (30 Days)	Transparent and Acceptable	32.05 ± 2.85	98%
3	3 months (90 Days)	Transparent and Acceptable	30 ± 2.0	97.6%