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FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILMS OF ZOLMITRIPTAN BY NATURAL POLYMERS

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ABSTRACT

The purpose of the present investigation was to formulate Fast Dissolving Oral Films of Zolmitriptan for the treatment of acute migraine attack. Films were prepared by solvent casting method using Natural Polymers Xanthan gum, Guar Gum, Sodium Alginate, Aloe vera Powder as the film forming polymer and PEG-400 as the plasticizer. Vanillin was used as taste masking agent in the formulations. Sodium Alginate has excellent film forming capacity with rapid hydration power which leads to rapid disintegration of film upon contact with saliva. The concentrations of the polymers and plasticizer were selected as independent variables. Eight formulations were prepared. The thickness, folding Endurance, disintegration time, % drug released and drug content were selected as dependent variables. The optimized formulation, F6 was found superior than remaining 7 batches. Among all the formulations, F6 has shown maximum drug release of 99.1±0.05% within 8 min and a very low disintegration time of 8.33±0.57sec due to super-disintegrant Sodium Starch Glycolate. Hence the films made of 2%w/v of Sodium Alginate and PEG-400 showed excellent film forming property with rapid drug release profile. FT-IR studies revealed that there was no physico-chemical interaction between polymer and drug. Stability studies revealed that optimized formulation was stable as the % drug release at the end of 3rd month was 99.1%. The observed independent variables were found to be most satisfactory formulation which demonstrates the feasibility of the optimization procedure in successful development of fast dissolving oral film containing Zolmitriptan by using Sodium Alginate, PEG-400 and Vanillin as key excipients.

Keywords: Fast dissolving films, Sodium Alginate, Sodium starch glycolate, Zolmitriptan.

INTRODUCTION

Fast dissolving Oral Films are the most advanced form of oral solid dosage form due to more flexibility and comfort. 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. The delivery system consists of a very thin oral strip. When these strips are placed sublingually the film rapidly hydrates and adheres on the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption. It gives quick absorption and instant bioavailability of drugs due to high blood flow, since the permeability of oral mucosa is 4-1000 times greater than that of skin. The absorption of the drug through the sublingual route is 3 to 10 times greater than oral route and is only surpassed by hypodermic injection. For these formulations, the small volume of saliva is usually sufficient to result in disintegration of films in the oral cavity.

The advantages of Fast dissolving Oral films over other oral dosage forms are: these are thin, elegant, unobstructive, better patient compliance, site specific, provides enhanced oral bioavailability of molecules that undergoes first pass effect and non invasive.

Zolmitriptan is a selective 5-hydroxytryptamine receptor subtype agonist indicated for the acute treatment of migraine attacks with or without aura in adults. Zolmitriptan is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. Zolmitriptan is an agonist for a vascular 5-hydroxytryptamine receptor subtype (probably a member of the 5-HT $_{ID}$ family) having only a weak affinity for 5-HT_{1A}, 5-HT_{5A}, and 5-HT_7 receptors and no significant affinity or pharmacological activity at 5-HT_2, 5-HT_3 or 5-

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HT_4 receptor subtypes or at alpha-l, alpha-2, or beta-adrenergic, dopamine-l, dopamine-2; muscarinic, or benzodiazepine receptors. Zolmitriptan binds with high affinity to human 5-HT_{111} and 5-HT_{ID} receptors leading to cranial blood vessel constriction [1-3].

Migraine is a condition, which requires immediate action. To achieve this the drug was formulated into Fast Dissolving Oral Films for Oral administration so that the onset of action is rapid. In the above dosage form Xanthan gum, Guar gum, Sodium Alginate and Aloe vera were used as film forming polymers. Poly ethylene glycol 400 as plasticizer, Sodium starch glycolate (SSG) as disintegrant, Vanillin as flavoring agent and sodium saccharin as sweetening agent.

MATERIALS AND METHODS

Zolmitriptan was obtained as gift sample from Dr Reddy's, Hyderabad, India. Xanthan gum, Guar gum, Sodium alginate and Aloe vera, Vanillin, SSG, Sodium Saccharin were obtained from SD Chemicals, Mumbai.

Method of preparation of Fast Dissolving Oral Films

Films were prepared 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 0.4 %, 0.7 %, 1.5 % and 2 % (w/v) solution respectively, PEG-400 was added to this polymer solution. Drug, Sodium starch glycolate, Vanillin were dissolved in water in another 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 dish mounted with aluminum foil of surface area 18 cm^2. It was dried for 24 hours at room temperature. The film was removed from the dish very carefully and observed for any imperfections. Film that was clear and bubble free was selected for further studies. Films of area 6 cm^2 (2 X 3) were cut and stored in a butter paper covered with aluminum foil and stored in a desiccator [4,5].

Evaluation:

Weight variation of the film: 2 x 3 cm^2 film was cut at five different places in the casted film. The weight of each film strip was taken and the weight variation was calculated.

Thickness of the film: The thickness of the film was measured using digital vernier caliper with a least count of 0.01 mm at different spots of the film. The thickness was measured at three different spots of the film and average was taken and SD was calculated.

Folding endurance: The folding endurance is expressed as the number of folds required to break the specimen or develop visible cracks. This gives an indication of brittleness of the film. A small strip of 2×3 square cm was subjected to this test by folding the film at the same plane repeatedly several times until a visible crack was observed.

pH studies: The pH was determined by dissolving a film in 2 ml of distilled water and then the pH of the obtained solution was measured by pH meter.

Drug Content uniformity: Drug content uniformity of all eight batches was determined by UV-Spectrophotometric method. For this, each strip at three different places equivalent to 2.5mg of drug was cut and dissolved in 50ml of 6.8Ph phosphate buffer solution with continuous stirring. This solution was filtered using Whattmann filter paper, and the filtrate was diluted to 100ml with the same buffer in a volumetric flask. This solution was analyzed by U.V Spectrophotometer and the absorbance was recorded at 223nm. Drug content was calculated by using calibration curve of drug.

Disintegration time: Test was performed using Disintegration test apparatus. 2×3 cm^2 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 ten times a minute. Time required by the film, when no traces of film remain above the gauze was noted and test was performed in triplicate.

***Invitro* Dissolution studies:** Dissolution study was carried out using USP type I (basket apparatus) with 300 ml of 6.8 pH Phosphate buffer as dissolution medium maintained at 37 $\pm 0.5^0$ C. Medium was stirred at 50 rpm for a period of 30 minutes. Samples were withdrawn at every 2 min interval up to 20 min, replacing the same amount with the fresh medium. Samples were suitable diluted with 6.8 pH and analyzed for drug content at 223 nm. Cumulative percent drug release of Zolmitriptan was calculated and plotted against time [6,7].

Data Analysis

To analyze the mechanism of the drug release kinetics of the dosage form, the data obtained were fitted to various kinetic equations of Zero order, First order, Higuchi model and Korsmeyer - Peppas model and plotted as:

1. Cumulative percent drug released Vs time(Zero order plots)
2. Log cumulative percent drug remaining Vs time(First order plots)
3. Cumulative percent drug release Vs square root of time(Higuchi plots)
4. Log cumulative percent drug release Vs log time(Korsmeyer-Peppas Plots).

RESULTS AND DISCUSSION

a) Determination of λ_{max}: $\lambda_{max}$of Zolmitriptan was found to be 223 nm as it shows maximum absorbance in this wavelength.

b) Calibration Curve of Zolmitriptan: Standard Calibration curve of Zolmitriptan was drawn by plotting

Absorbance vs Concentration. The λ_{max} of Zolmitriptan in 6.8 pH Phosphate buffer solution was found to be 223nm. Conditions were tabulated in the table no.2.Standard calibration curve of Zolmitriptan in 6.8 pH phosphate buffer solution was shown in fig1.

FT-IR Spectroscopy

The FT-IR spectrum of the pure drug was found to be similar to the standard spectrum of Zolmitriptan. The spectrum of Zolmitriptan showed the following functional groups at their frequencies mentioned in the table no 3.

Compatibility Studies

From the FT-IR Spectra of pure drug and the combination spectra of drug with the polymers, it was observed that all the characteristic peaks of drug are present in the combination spectra as well thus indicating the compatibility of the drug with the polymers used. The individual FT-IR Spectra of Zolmitriptan, Zolmitriptan+sodium alginate as well as combination of final optimized formulation (F6) are shown in fig 2 & table no 3.

Weight uniformity test

The weights of the films were found to be in the range of 30±0.24mg to 51.47±0.63mg. The results of average weight of all films were summarized in fig no.3.

Physical appearance and surface texture

The observation by visual inspection of films and by feel or touch, suggests that the films are having smooth surface and they are elegant enough to see.

Thickness of films

The thicknesses of the films were in the range of to 0.051±0.007mm to 0.037±0.002mm. The results of average thickness of all films were summarized in fig no.3.

Folding endurance: Folding endurance of the films was found to be in the range of 13.60±1.31 to 38.62±1.52.The results of average folding endurance of all films were summarized in fig no.3.

Surface pH: The surface pHs of all the films were found to be near to be of neutral pH i.e 7.

Drug content uniformity test

The drug content uniformity was performed by taking three films in each formulation trial and the average drug content was calculated. The results were found to be in the range of 97.56±0.31% to 98.90±0.26%. The results of average drug content of all films were summarized in fig no.3.

***In vitro* disintegration test**

The disintegration times of the prepared films were in the range of 8.33±0.57 to 12±1.73sec. The results of average disintegration time of all films were summarized in fig no.3.

***In-vitro* dissolution studies**

Zolmitriptan FDOF dissolution study was conducted in 6.8pH phosphate buffer solution as this was similar to the pH of simulated salivary fluid. A modified dissolution methodology was followed to simulate the conditions of the oral cavity. The dissolution volume consists of 300ml of 6.8pH phosphate buffer solution at 37±0.5˚C, which was rotated at 50rpm. Zolmitriptan FDOF from each formulation was carried out in 6.8 pH phosphate buffer solution for 20min. The data of dissolution studies were summarized in Fig no.4. The dissolution study was conducted for 20 min. The drug release was found to be in the range of 98±0.2 to 99.96±0.01% and the % drug release was maximum. The plots of % cumulative drug release versus time (min) were plotted and depicted as shown in Fig no.4. The formulation F6 showed higher drug release of 99.96±0.01% revealing that films made with concentrations of Sodium Alginate and PEG-400 viz., 2%w/v was the optimized formulation as it shows a higher drug release in the dissolution study. As higher dissolution rate aids in faster onset of action, F6 was chosen as the optimized formulation.

Data analysis (Curve fitting analysis)

For analyzing the mechanism of the drug release kinetics of the dosage form, the data obtained were fitted to various kinetic equations of Zero order, First order, Higuchi model and Korsmeyer - Peppas model. The regression coefficient was calculated. Graphs of kinetic models were plotted with suitable data which was summarized in table no.4.

Curve fitting data of different kinetic models

The linear regression coefficient of each kinetic model was calculated and pattern of drug release from dosage form is predicted. The regression coefficients of First order plots, Higuchi and Korsmeyer-Peppas plots were higher when compared to zero order plots. The results are summarized in table no.4.

Stability studies

The formulation of F6 was evaluated for stability studies which was stored at 40˚C / 75% RH for 3 months and evaluated for their physical appearance, drug content and *invitro* disintegration time and % drug release at the end of 1st and 3rd month. The results were summarized in table no 5.

CONCLUSION

In the present work, Zolmitriptan Fast Dissolving Oral Films were prepared by Solvent Casting method using Natural Polymers and PEG-400. Zolmitriptan was readily soluble in water but its bioavailability is low. It undergoes first pass metabolism. Hence it was formulated into FDOF to improve its bioavailability by avoiding first pass metabolism.

Table 1. Composition of different batches of Fast Dissolving Oral films of Zolmitriptan

S.No	Ingredients (mg/film)	F1	F2	F3	F4	F5	F6	F7	F8
1	Zolmitriptan	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
2	Xanthan gum*	0.4	0.7	-	-	-	-	-	-
3	Guar Gum*	-	-	0.4	0.7	-	-	-	-
4	Sodium Alginate*	-	-	-	-	1.5	2	-	-
5	Aloe vera Powder*	-	-	-	-	-	-	1.5	2
6	PEG-400**	20	20	20	20	20	20	20	20
7	Vanillin	2	2	2	2	2	2	2	2
8	Sodium Starch Glycolate	1	1	1	1	1	1	1	1
9	Sodium Saccharin	1	1	1	1	1	1	1	1
10	Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

* = Expressed as %w/v

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

Table 2. Calibration data parameters for Zolmitriptan in buffer

Optical characteristics	Zolmitriptan in 6.8 pH Phosphate Buffer
λ_{max}(nm)	223
Beer's law limit (µg/ml)	5 to 25
Correlation coefficient	0.999
Slope(m)	0.156
Intercept(c)	0.005

Fig.1. Standard calibration curve of Zolmitriptan in 6.8pH Phosphate buffer solution

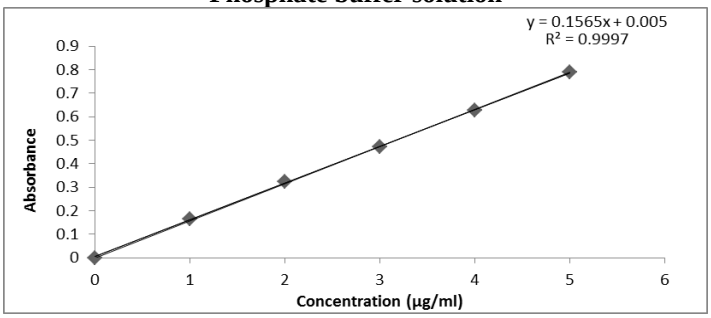


Table 3. FTIR interpretation results

Functional Groups	Standard Peaks	Type of Vibration	Assessed Peaks In cm^{-1}		
			Drug	Drug + Na-Alg	F6
Aromatic Compound	1450-1600cm^{-1}	C=C stretch	1468	1471	1457
RR' N-H	3310-3850cm^{-1}	N-H stretch	3852.98	3988.96	3983.18
C-N	1000-1400cm^{-1}	Stretch	1088.86, 1252.82	1086.93,1249.93	1086.93,1221.96

Table 4. Data of regression coefficient of different kinetic models

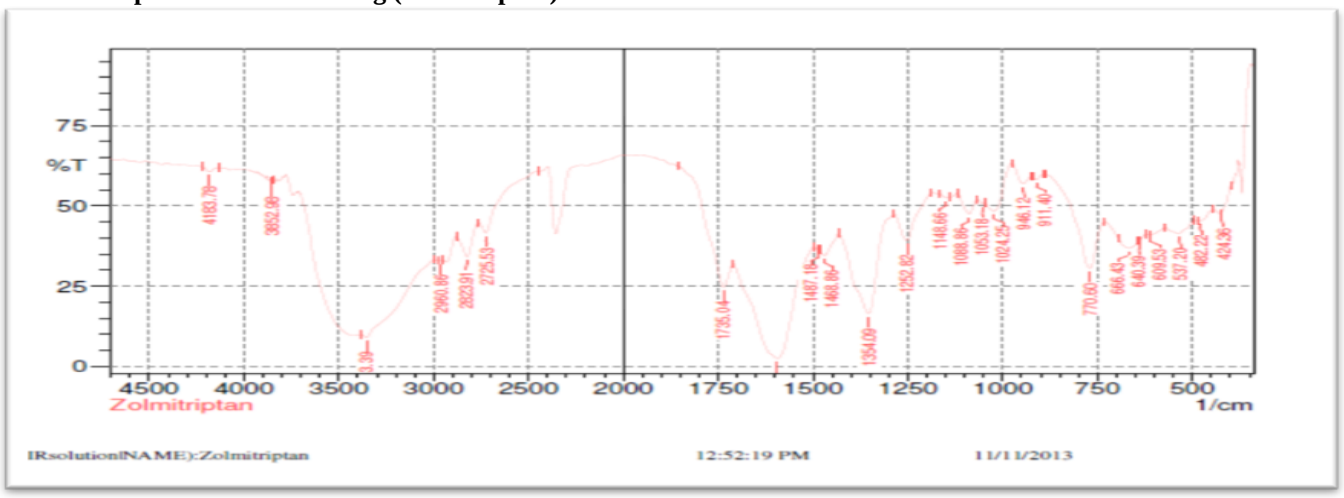
Formulation code	Zero order $(R)^2$	First order $(R)^2$	Higuchi $(R)^2$	Korsmeyer-Peppas $(R)^2$
F1	0.804	0.977	0.932	0.898
F2	0.759	0.965	0.925	0.965
F3	0.898	0.970	0.945	0.957
F4	0.823	0.963	0.913	0.890
F5	0.972	0.899	0.970	0.985
F6	0.936	0.918	0.979	0.964
F7	0.974	0.867	0.975	0.989
F8	0.913	0.945	0.976	0.967

Table 5. Stability data of formulation F6

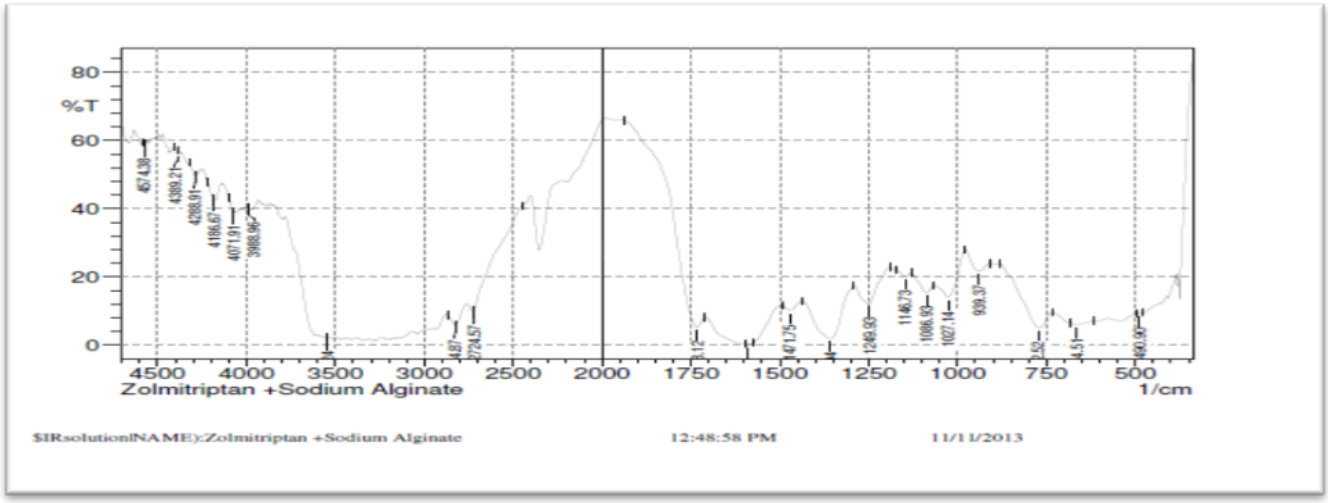
Time in months	Formulation F6 stored at 40˚C / 75% RH		
	Physical appearance	Disintegration time in sec	% Drug release
Initial	Smooth & elegant	8.33±0.57	99.96± 0.01
After 1 month	Smooth & elegant	8.89±0.08	99.4±0.04
End of 3rd month	Smooth & elegant	9.24±0.25	99.1±0.05

Fig 2. Drug and excipients compatibility by FTIR

2A.FT-IR Spectrum of Pure Drug (Zolmitriptan)



2B.FT-IR Spectrum of Zolmitriptan+ Sodium Alginate



2C.FT-IR Spectrum of Optimized Formulation F6

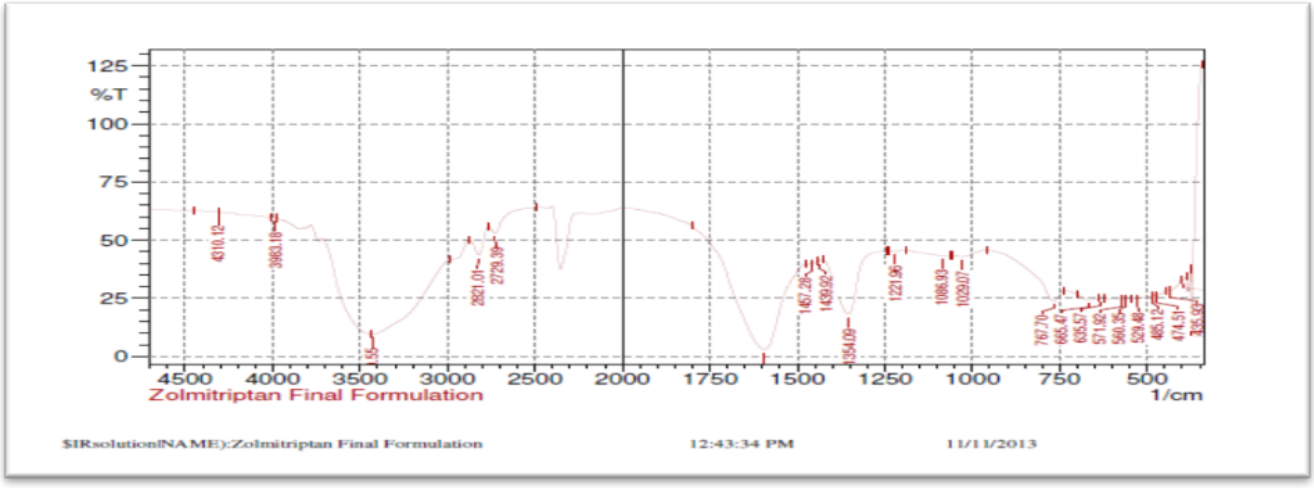


Fig 3. A. Weight variation B. Thickness C. Folding endurance D. Surface pH E. Drug content F. Disintegration time

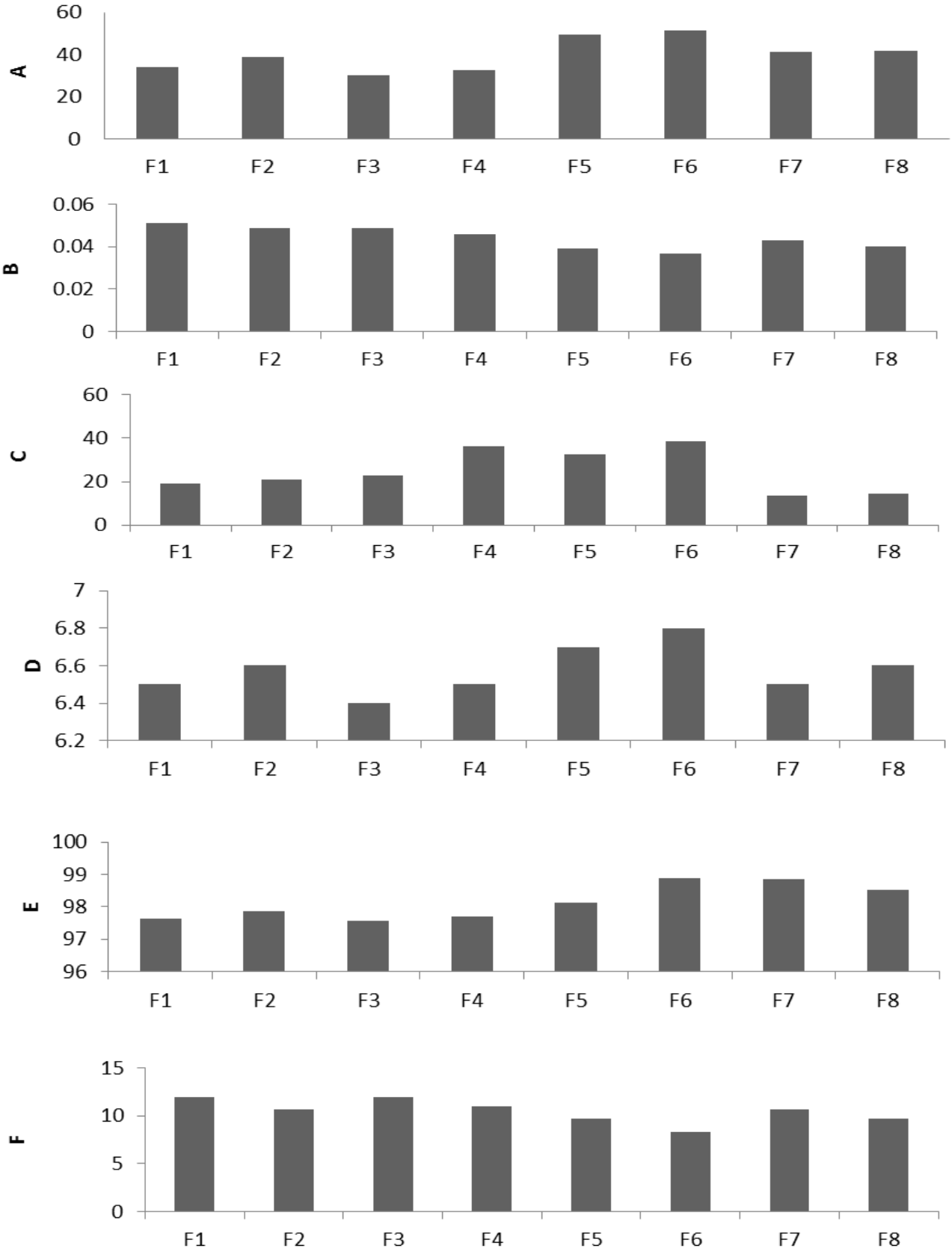


Fig 4.*Invitro* drug release data of formulation F1 to F8

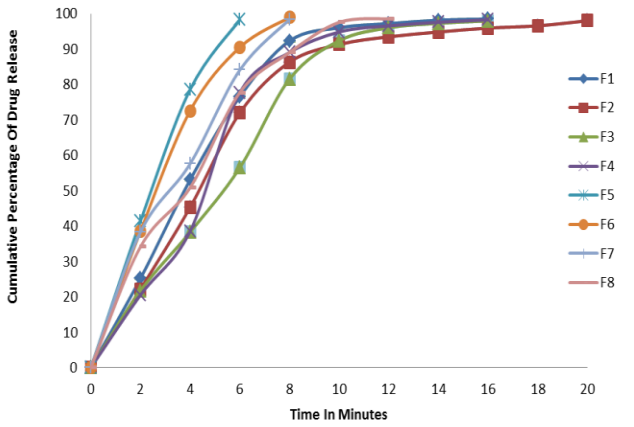
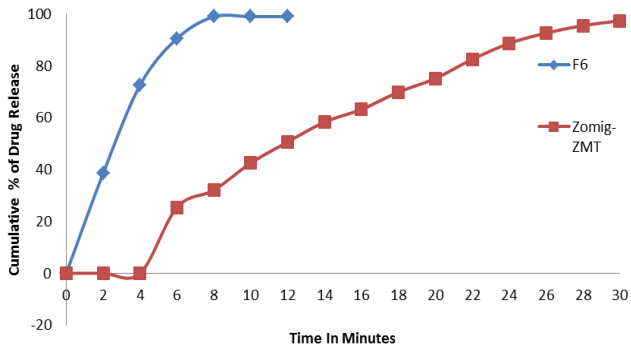


Fig 5. Comparative Study of F6 with Marketed Product Zomig-ZMT



FT-IR Spectra of Zolmitriptan with polymer doesn't show profound shift in peak which indicates compatibility. The prepared films were Smooth and Elegant. Formulated films gave satisfactory results for various evaluation parameters like physical appearance and surface texture, weight uniformity, thickness uniformity, folding endurance, surface pH, drug content uniformity, *invitro* disintegration time, *invitro* drug release. The low standard deviation values for average thickness, weight variation and drug content of the prepared films indicate uniformity within the batches prepared.

Based on *invitro* disintegration time, all the formulations were within the limit(less than 30sec) of CDER guidance for oral disintegrating tablets. All the films disintegrated within 15sec.The formulation F6 showed maximum %drug release of 99.96±0.01% in 8min.The final optimized formulation (F6) was compared with marketed product of Zolmitriptan tablets which shows 97.4±0.23% drug release in 30 mins. From this observation it was concluded that the formulated film of Zolmitriptan (F6) were superior and effective in achieving patient compliance.

All the prepared films showed First order kinetics. Higuchi plots revealed that the mechanism of drug release was diffusion and Peppa's plot indicates fickian diffusion transport. Accelerated stability studies of optimized formulation F6 indicates that there is no significant change in drug content, *invitro* disintegration time and % drug release. From the present study, it may be concluded that Fast Dissolving Oral films of Zolmitriptan can be prepared by solvent casting method using Natural Polymers as the film forming polymer. At 2%w/v of Sodium Alginate with PEG-400 showed the least disintegrating time of 8.33±0.57sec and the highest release of 99.96±0.01 % of the drug in 8min.

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