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Formulation and Optimization of Zolmitriptan Oral Fast Dissolving Films

M. Venkata Ramana, G. N. S. S. Chandra Sekhar*, R. Anji Reddy, M. Maheswara Reddy, G. Vamsi and Rama Rao. N

Department of Pharmaceutics, Chalapathi Institute of Pharmaceutical Sciences, Lam, Guntur, India

Abstract : The present research work deals with development and optimization of oral fast dissolving films of zolmitriptan to improve bioavailability and patient compliance.It is anti-migraine drug which has oral bioavailability of 45% due to hepatic firstpass metabolism. Oral fast dissolving films of zolmitriptan were prepared by solvent casting method using HPMC E-5 as a film forming polymer, propylene glycol as a plasticizer, sodium starch glycolate as a superdisintegrant and aspartame isadded as sweetener. Theprepared film characterised by FTIR showed no incompatibility between drug and polymer. A 2^3 factorial design is employed for the optimization of formulation considering concentration of polymer, plasticizer and superdisintegrant as independent variables with drug release, disintegration time, folding endurance as dependent variables. The formulations F1-F8 are made by varying the levels of independent variables and evaluated for disintegration time, dissolution rate and foldingendurance. The results are treated by DesignExpert softwareto optimise the oral fast dissolving film. Theoptimised film isanalysed by X-ray diffraction shows crystalline to amorphous transformation of drug and DSC thermogram shows a broad peak further conforms the amorphous nature of drug. It was found that enhancing the polymer and plasticizer concentrations shows negative effect on disintegration time and drug release. But when the concentration of superdisintegrant was increased it had a positive effect on drug release and disintegration time. From the results obtained the optimized formulation was prepared with 4% of HPMC E5, 1.5% of propylene glycol and 4%of sodium starch glycolate showed disintegration time 10 sec, drug release 93.15% and folding endurance of 260 times.

Key words : Zolmitriptan, Hydroxyl Propyl Methyl Cellulose, Propylene glycol, Sodium starch glycolate, Aspartame.

Introduction:

Fast dissolving films are most advanced form of solid oral dosage form due to its flexibility.It improve efficacy of active pharmaceutical ingredient (API) by dissolving in the short time in oral cavity after the contact with less amount of saliva as compared to mouth dissolving tablet.[1] The oral cavity covers the cheek, lips, tongue, hard palate and soft palate. The lining of the oral cavity is referred to as the oral mucosa.[2] The delivery

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system is simply placed on the patient tongue or any oromucosal tissue. Instantly wet by saliva due to the presence of hydrophilic polymer, the film rapidly hydrates and dissolves to release the medication for oromucosal absorption.[3]Migraine attacks typically unfold through a sequence of events that occur over the time course of several hours to days, and typically progresses through four phases.[4]Treatment for migraine headaches can be divided into two broad categories, acute treatments that are taken once a migraine begins, in order to reduce the intensity or abort the attack. Triptans are serotonin (5-HT) analogs that are selective for the 5-HT 1B/1D/1F subtype receptors.The objective of the study is to develop oral fast dissolving films (OFDF's) for Zolmitriptan in order to improve the bioavailability. The oral bioavailability of zolmitriptan is 45% due to hepatic first pass metabolism.[5]Zolmitriptan Oral Fast Dissolving Films (ZOFDF's) is systemically optimized using 2^3 full factorial design.

Materials and Methods:

Materials:

Zolmitriptan obtained as gift sample from APOTEX INC (Bengaluru), and HPMC E5 is procured from COLORCON (Mumbai), and remaining all chemicalsare procured from local SD Fine (Mumbai) distributor. All chemicals used are laboratory grade.

Preformulation studies:

Preformulation involves the application of pharmaceutical principles to the physicochemical properties of drug substance and is characterized with the goal of designing optimum drug delivery system.[6]It pays a significant role in anticipating the formulation problems. Several formulation trails are made in order to obtain a good film by varying the ratios of HPMC, PG, and SSG. HPMC used between 2% to 8%, PG used between 1% to 5% and SSG used between 1% to 6%.

Table-1:Formulation table of zolmitriptan oral fast disintegrating films using 2^3 factorial design

S.No	Ingredients	Formulation codes							
		F1	F2	F3	F4	F5	F6	F7	F8
1	Zolmitriptan (mg)	20	20	20	20	20	20	20	20
2	HPMC E 5 (%)	2	8	2	8	2	8	8	2
3	Propylene glycol (ml)	1	1	5	1	1	5	5	5
4	Sodium starch glycolate (%)	6	1	1	6	1	1	6	6
5	Aspartame (mg)	15	15	15	15	15	15	15	15
6	Water (ml)	10	10	10	10	10	10	10	10

Preparation of fast disintegrating films:

Fast disintegrating films of zolmitriptan was prepared by solvent casting method. The composition of the formulations is presented in table-1. The required quantity of polymer (HPMC) and plasticizer (Propylene glycol) was dissolved insmall quantity of distilled water. This polymeric dispersion was stirred for 1 hr using magnetic stirrer. In another beaker the aqueous solution was prepared by dissolving specified quantities of drug (Zolmitriptan), super disintegrant (Sodium starch glycolate), Aspartame in specific proportion[7]. The resulting aqueous solution was added to polymeric dispersion and stirred for 1 hr. Aspartame added as sweetner. After removal of air bubbles, the polymeric solution containing drug was casted on the film former (VJ instruments, Mumbai) and temperature is maintained at 50ºC. Dried film was carefully removed from film former and trimmed into 10×10 cm^2 size. Trimmed films were stored in air tight container stored in desicator.[8] All the formulations were stored at a temperature (25$\pm$ 0.5ºC) in air tight containers.

2^3 factorial design for formulation of films:

Statistical analysis of the experimental work was carried out using Design Expert 10 portable software.[9] A 3-factor, 2-level full factorial design was used to derive the second order polynomial equation.

Concentration of HPMC E 5 (X_1), PG (X_2), SSG (X_3) are selected as independent variables while disintegration time (Y_1), *invitro* drug release (Y_2), folding endurance (Y_3) were selected as dependent variables.

Characterization of ZOFDF's:

Morphological Properties:

Morphological properties such as the homogenous nature of film, colour, transparency and surface of ZOFDF'S are tested visually.

Uniformity of film Thickness:

ZOFDF's thickness was measured by using micrometer screwgauge at 5 different strategic locations. This helps in determining the uniformity of thickness of oral fast disintegrating films which directly relates to the accuracy of the dose.**[10]**

Percentage moisture loss:

The percentage moisture loss studies were carried to check film physical stability. Initially weighed ZOFDF's of predetermined size ($3\times3cm^2$) was placed in a desiccators containing anhydrous calcium chloride (inside the desiccators) for three days. The films were removed and weighed again to calculate the percentage moisture loss by using following formula.[11]

% Moisture loss = (Initial weight – Final weight / Initial weight) × 100

I) Percentage moisture uptake:

Weighed films are kept in desiccators at room temperature for 24 hours. These are then taken out and exposed to 84% relative humidity using saturated solution of potassium chloride in desiccators, until a constant weight is achieved. Percentage moisture uptake is calculated as given below.[12]

%Moisture uptake = (Final weight – Initial weight / Final weight) × 100

Folding endurance:

Folding endurance provides the information regarding the flexibility as well as the physical ability of the OFDF'S. It was measured by firmly folding OFDF'S repeatedly at the middle. The number of folds on the same crease, required to produce crack in the film was noted as the value of folding endurance.[13]

***Invitro* disintegration time:**

This method was performed by using Petri dish. In this method Petri dish was filled with 10ml of pH 6.8 phosphate buffer and the OFDF'S was carefully placed at the centre of the Petri dish. Time taken by the film to disintegrate is measured and the test is performed in triplicate manner.[14]

Surface pH:

OFDF'S to be tested was cut into 2×2 cm^2 square shaped and is placed in a Petri dish and moistened by 1 ml of water and kept for 1 min. surface pH of the OFDF's was measured by using a pH meter (ELICO-L1120). An average of 3 trials was taken as surface pH. For all the formulations, surface pH was calculated.[15]

Drug content uniformity:

Three OFDF's were trimmed from 3 different places of the total casted film. Each film was separately dissolved in a volumetric flask containing 100 ml of pH 6.8 phosphate buffer. Three volumetric flasks were shaken until OFDF's gets dissolved. All the solutions were filtered and samples were analysed by using double beam UV spectrophotometer using plain placebo solution as blank. An average of the 3 trails was taken as drug content in each OFDF's. The same procedure was repeated for the remaining formulations. [16]

***Invitro* dissolution rate:**

Invitro dissolution studies were carried out in USP type I apparatus (basket), 900 ml of phosphate buffer pH 6.8 was used as dissolution media at 37±0.5°C. 2×2cm^2 OFDF's was placed in dissolution basket. Dissolution was carried out by withdrawing aliquot of 5ml samples at regular time intervals 1, 2, 3, 4 and 5min time intervals and the fresh medium was replaced. Samples were filtered and diluted suitably and analysed by using a UV spectrophotometer at 223nm.[17]

FTIR studies:

As a part of the preformulation studies, drug-polymer interaction study was performed by using Fourier Transform Infrared Spectroscopy [FTIR].[18] The FTIR spectra of Zolmitriptan, HPMC E5, and their physical mixture were recorded individually. The samples were scanned in the range of 400-4000cm^{-1}.

Differential scanning calorimetry (DSC):

Pure zolmitriptan, and the prepared film subjected to DSC studies using TA instruments Q20 model. Empty Aluminium sample pan was used as reference material. Samples are scanned at the rate of 10^0 C/ min from room temperature to 300° C where in nitrogen gas is used as purge gas at a flow rate of 50mL/min.

Powder X-ray diffraction (XRD) studies:

Pure zolmitriptan, and the prepared film were subjected to XRD studies. The scanning rate employed was 2° per min, and samples were analysed between 2θ angles 10-80° a voltage of 40kB and a current of 30aM.

Results and Discussion:

Table-2:Evaluation Parameters of oral fast dissolving film:

Formulation code	% Moisture loss	% Moisture absorption	Disintegration time (sec ± SD)	%Drug content (%±SD)	Folding Endurance (folds)
F1	1.17 ± 0.48	2.61 ± 0.08	08± 0.04	96.36± 2.46	200±2
F2	1.47 ± 0.37	2.20 ± 0.09	16 ±0.24	75.10 ± 1.64	260±3
F3	1.98 ± 0.50	2.53 ± 0.10	15 ± 0.03	88.60 ± 1.28	280±1
F4	1.21 ± 0.08	1.82 ± 0.97	10± 0.28	97.22 ± 1.44	220±2
F5	1.88 ± 0.55	1.63 ± 0.89	12± 0.24	83.65 ± 0.42	270±4
F6	1.66 ± 0.43	1.91 ± 0.54	12± 0.01	90.81 ± 1.09	280±2
F7	1.98 ± 0.51	2.65 ± 0.08	11± 0.03	98.75 ± 0.78	280±3
F8	2.23 ± 0.53	2.53 ± 0.06	10± 0.10	98.45 ± 0.91	260±1
Mean±SD (n=3)					

Drug content uniformity:

Zolmitriptan in all the eight formulations is in the range of 95.32 to 99.81%. Thus all the formulations were within the specification limits (85 % 115%). The result of drug content studies is presented in table-2.

Percentage moisture uptake:

Percentage moisture uptake gives the information about the stability of the oral films. As the percentage moisture uptake is more, less will be the stability of the film. percentage moisture uptake values are shown in table-2. It is clear that as the polymer concentration increases moisture absorbing capacity also increases, which finally influence the stability of the film.

Percentage moisture loss:

All the eight formulations are subjected to the percentage moisture loss studies in order to know the amount of moisture present in the oral films after complete drying which alters the stability of films. Amount of moisture loss was calculated and the values are shown in table-2.

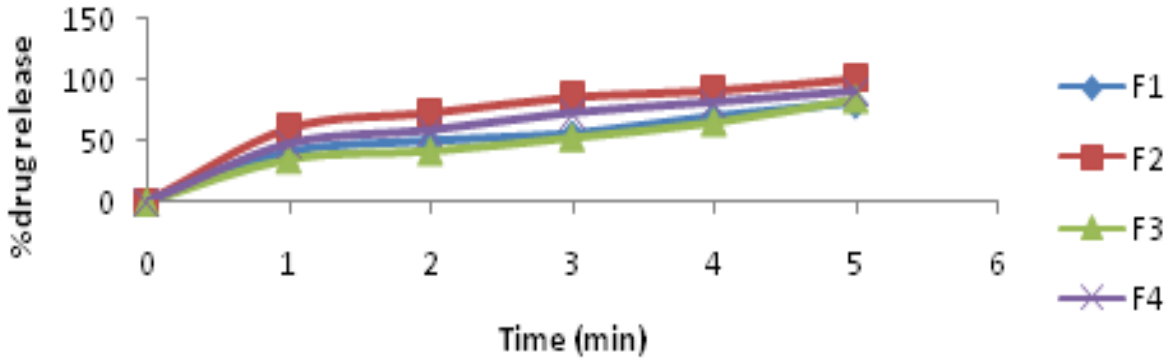
***Invitro* disintegration time:**

The disintegration time was calculated by petri dish method. The disintegration time for all eight formulations ranged from 8 to 16sec as shown in table-2. From the results it is evident that at higher concentration of superdisintegrant the film takes less time to disintegrate. Thus addition of superdisintegrant helps the faster breakdown of the film and hence fast release is obtained.

***In vitro* dissolution study:**

The dissolution of Zolmitriptan oral fast disintegrating films were carried out in USP I basket type apparatus. Dissolution study for all eight formulations was performed for 5 min. The results wereshown graphically in figures 1. From the results it can be said that as the concentration of polymer and plasticizer increases drug release decreased.

***Graph-1: Invitro* release studies of fast dissolving oral films of Zolmitriptan:**



Folding endurance:

Folding endurance gives an indication of brittleness of the film. The value depends upon the hydrophilic polymer and plasticizer concentrations used. Folding endurance for all eight formulations was found to be more than 200 times, as shown in table-2.As the concentration of plasticizer increases, folding endurance also increases. But from the contour plot (shown in fig-3) it is clear that as the concentration of PG increases disintegration time increases and as a result drug release decreases.

Surface pH:

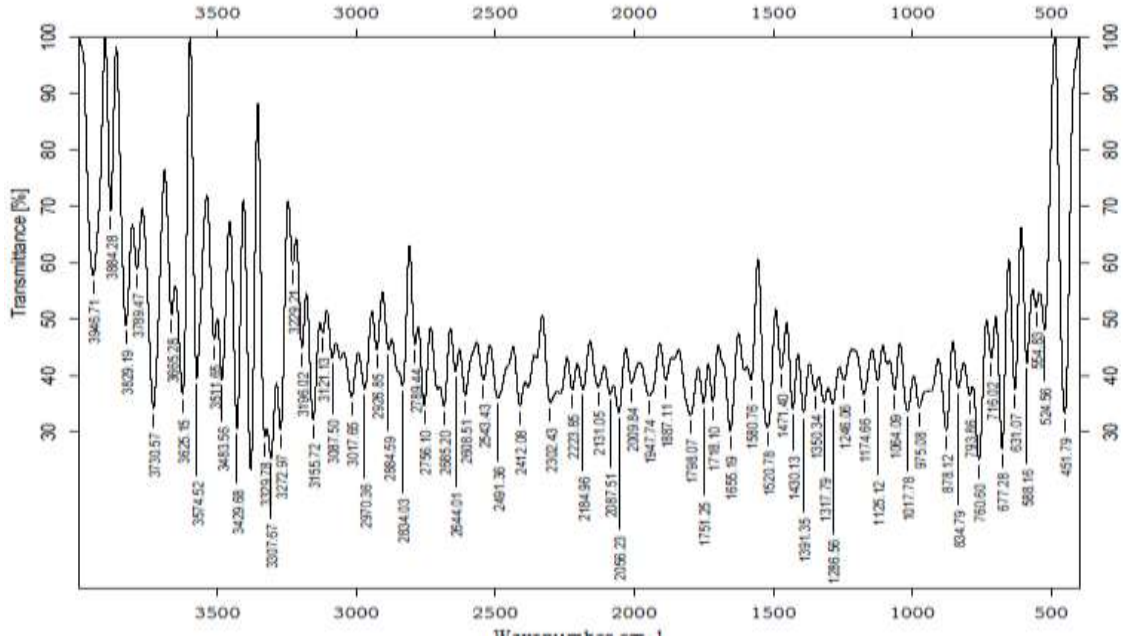
The prepared formulations are analysed for surface pH and all the formulations showed pH between 6.6 to 7 indicates there will not be much change in mouth feel.

Fourier Transform Infra-Red spectroscopy (FTIR):

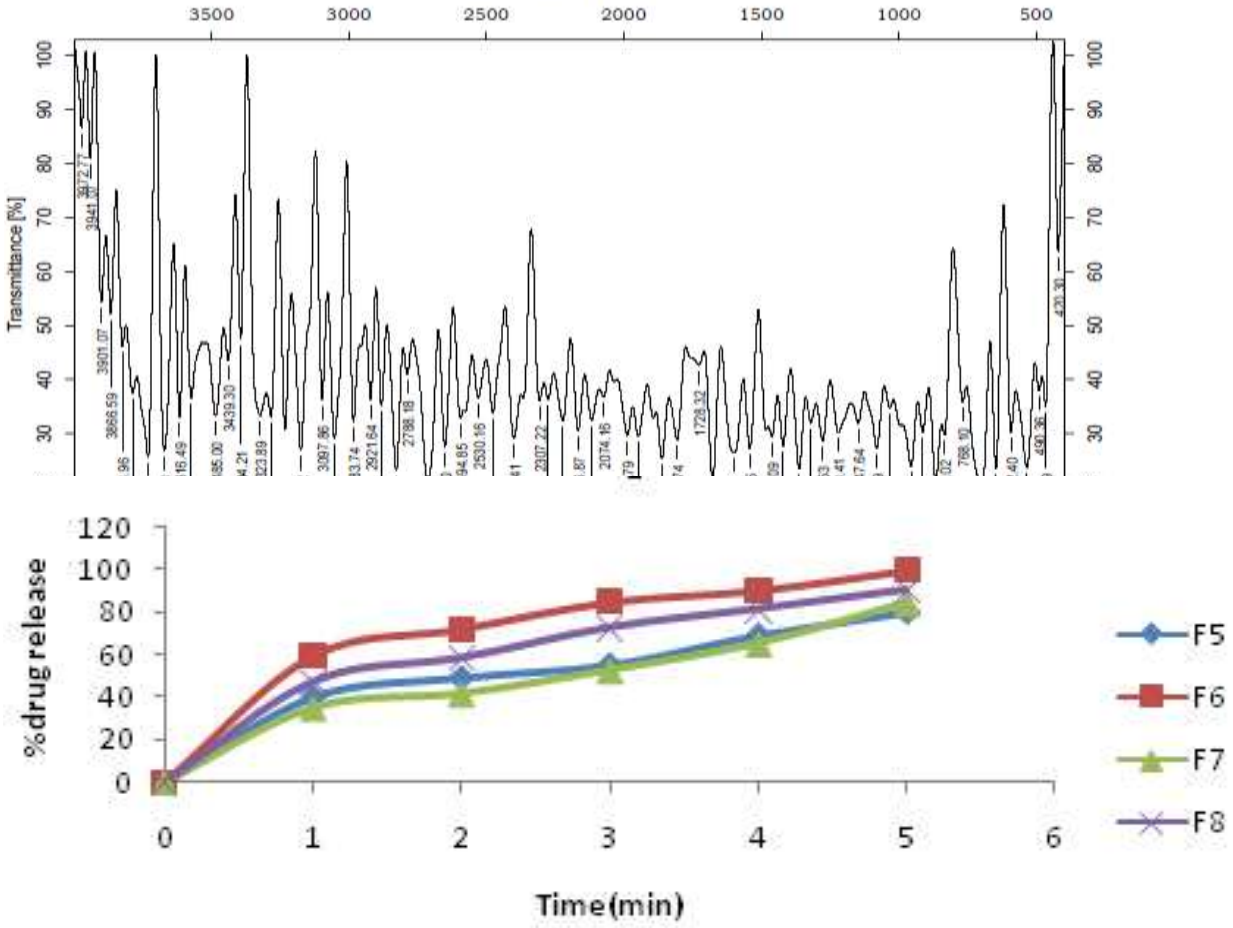
The FTIR spectra of pure zolmitriptan displayed bands at 3329.43 cm^{-1} due to N-H stretch, at 1751.83 cm^{-1} due to C=O stretching, at 1430.36 cm^{-1} due to heterocyclic C=C stretching. The spectra also showed bands at 1317 cm^{-1} due to C-H bending.

The FTIR spectrum of film containing zolmitriptan exhibited characteristic bands consistent with the molecular structure of zolmitriptan such as bands at 3322.43 cm^{-1} due to N-H stretch, at 1741 cm^{-1} due to C=O stretching, at 1423.36 cm^{-1} due to heterocyclic C=C stretching, at 1314 cm^{-1} due to C-H bending.

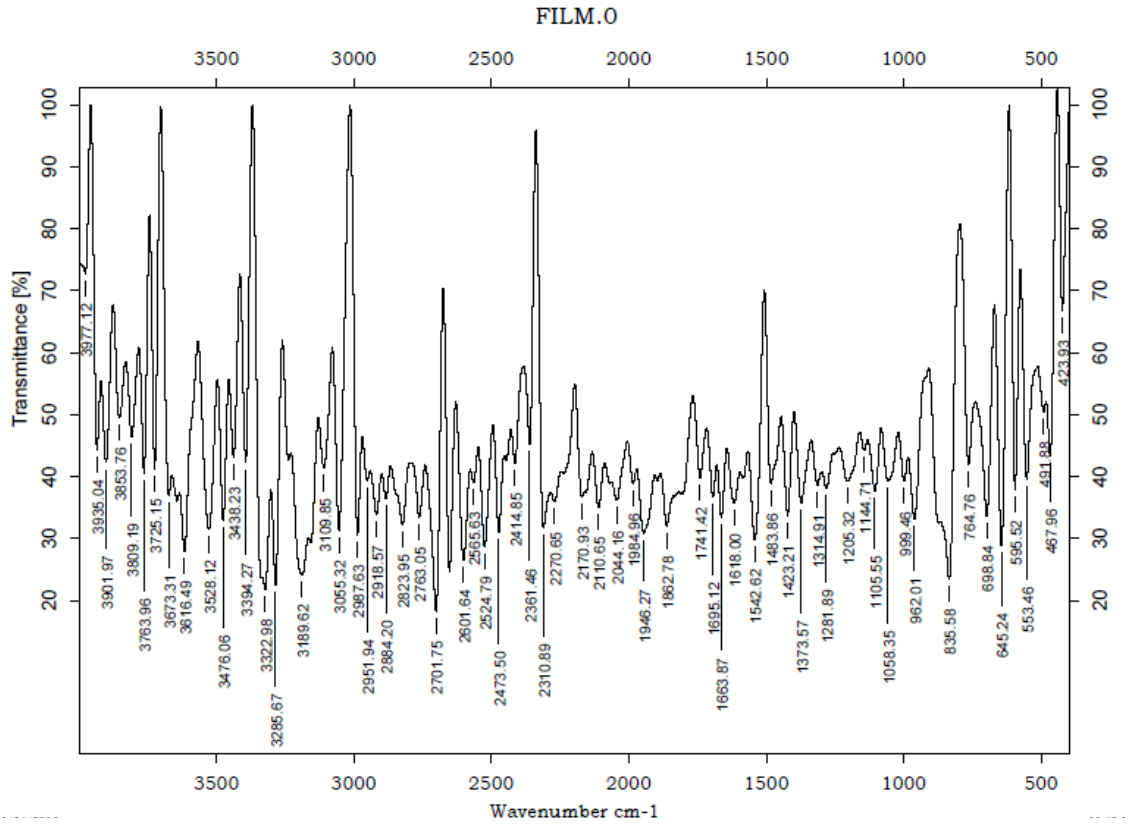
Graph-2: FTIR: spectra of zolmitriptan pure drug:



Graph-3: FTIR spectra of HPMC E 5



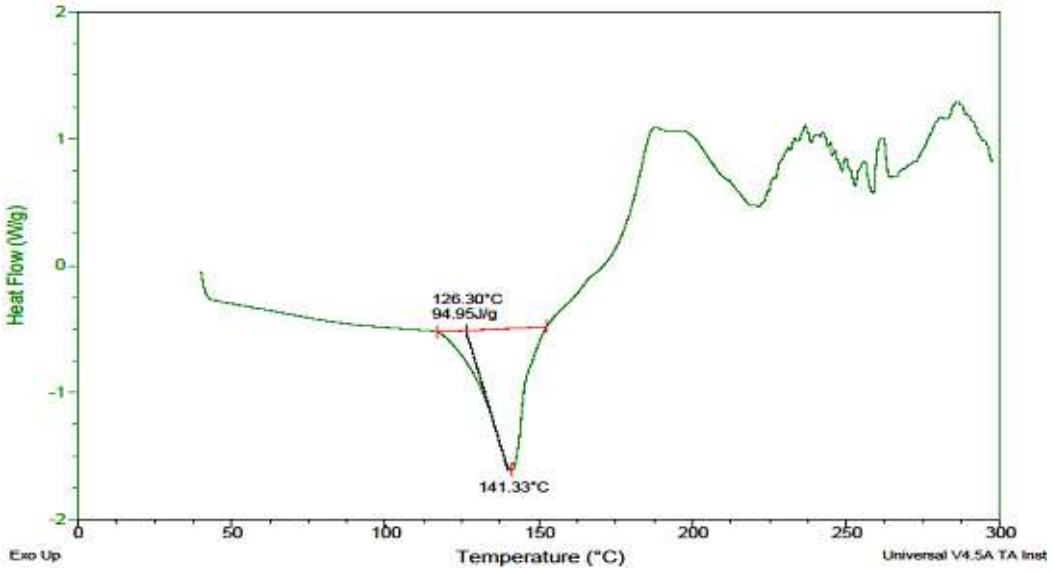
Graph-4: FTIR spectra of zolmitriptan film



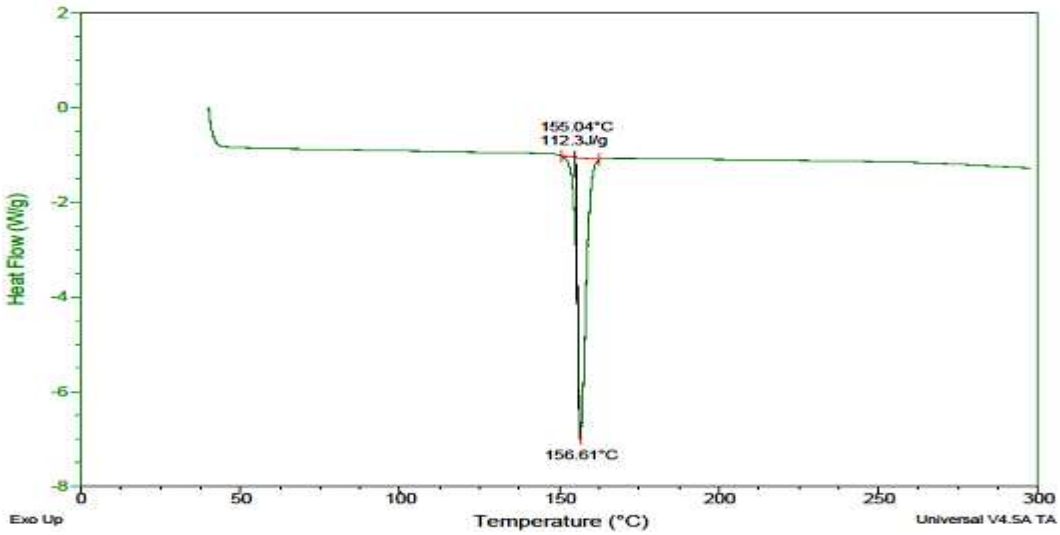
Differential scanning calorimetry (DSC):

Zolmitriptan shows sharp endothermic peak at 156.6 C, where as Zolmitriptan in the prepared film shows broad endothermic peak at 141.3 C indicates transformation from crystalline to amorphous nature.

Graph-5: DSC spectra of zolmitriptan oral film



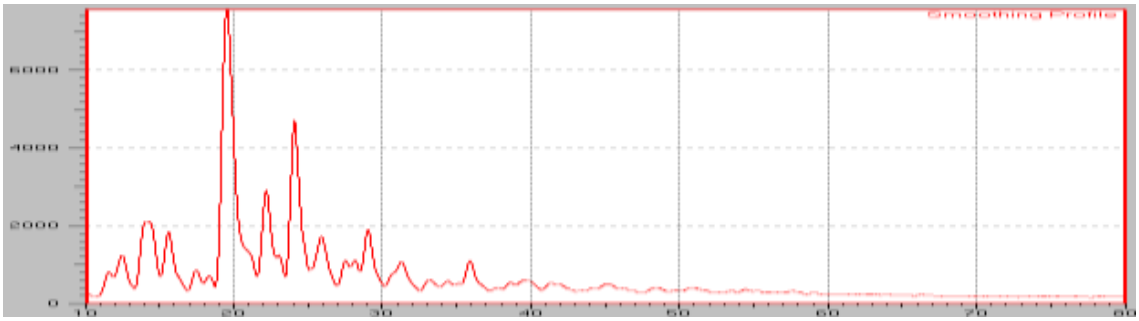
Graph-6: DSC spectra of zolmitriptan pure drug



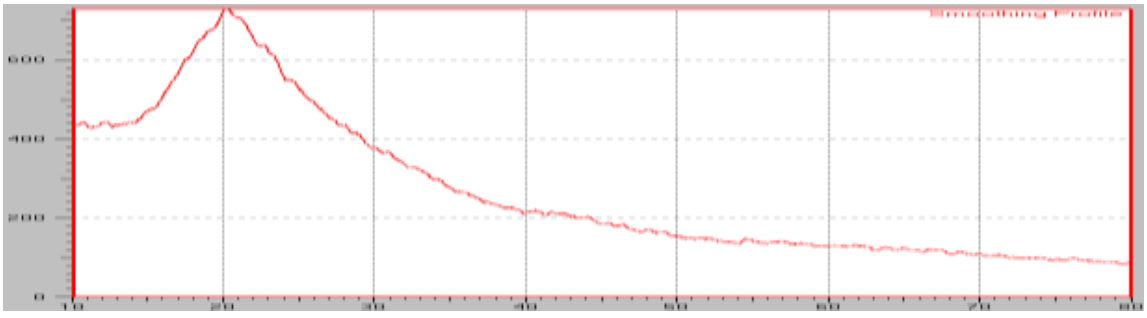
Powder X-ray diffraction (XRD) studies:

The X-ray diffractogramof zolmitripan shows sharp peaks at 14°, 19°, 24° indicates crystalline nature of the drug, where as the prepared film shows single broad peak at 22°further conforms the transformation of crystalline to amorphous nature of the drug in the prepared films.

Graph-7:XRD:Oral fast dissolving film



Graph-8:XRD:Zolmitriptan pure drug



Fitting of the model:

2^3 factorial experimental design was selected and as required 8 formulation batches were prepared. The ranges of Y1, Y2 and Y3 are 8-17sec, 75.10-98.75% and 200-280 times respectively. For all the responses observed for 8 formulations prepared were simultaneously fitted to linear, 2F1, quadratic and cubic models using Design expert. It was observed that the best fitted model were 2F1. A positive value represents an effect

that favours the optimization, while a negative value indicates an inverse relationship between the factor and response.

Response 1:Effect on disintegration time: The model purpose the following polynomial equation for disintegration time.

Disintegration(Y_1) = + 11.10000 + 0.712500 * HPMC + 1.000000 * PG - 0.933333 * SSG - 0.187500 * HPMC * PG + 0.016667 * HPMC * SSG.

Where, Y1 is disintegration time, X_1 is the concentration of polymer, X_2 is the concentration of plasticizer and X_3 is the concentration of superdisintegrant. The model F-value 0.0406 indicates the model is significant ($p < 0.05$). A positive value in above equation represents the synergic effect of the independent variable and a negative value represents the antagonistic effect.

Table-3: Response 1: Effect on disintegration time:

Source	Sum of squares	D f	Mean squares	F value	p-value Prob>F
Model	49.63	5	9.93	2.15	0.3477
X_1	3.13	1	3.13	0.675	0.4975
X_2	0.125	1	0.125	0.027	0.8845
X_3	36.13	1	36.13	7.81	0.1077
X_1X_3	0.125	1	0.125	0.027	0.8845
X_1X_2	10.12	1	10.12	2.19	0.2771

Figure-1: Invitro **disintegration time:**

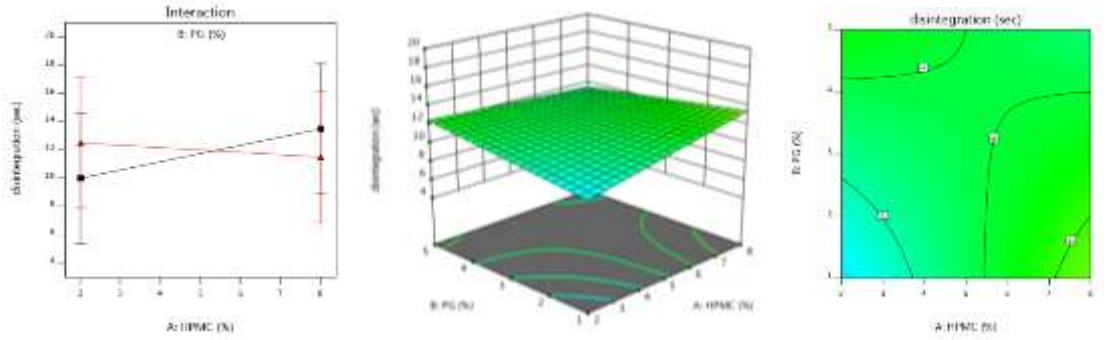


Fig-1: Plots showing interaction between two factors (A&B) and Contour plot showing effect of HPMC on disintegration time of film

Response2: Effect on drug release: The model purpose the following polynomial equation for drug release.

Dissolution(Y_2)= + 78.88000 – 1.23000 * HPMC + 2.01333 * PG + 3.27000 * SSG + 0.183333 * HPMC * PG + 0.130000 * HPMC * SSG – 0.430000 * PG *SSG.

Where, Y2 is drug release, X_1 is the concentration of polymer, X_2 is the concentration of plasticizer and X_3 is the concentration of superdisintegrant. The model F-value 0.0363 indicates the model is significant ($p<0.05$). A positive value in above equation represents the synergic effect of the independent variable and a negative value represents the antagonistic effect.

Table-4: Response 2: Effect on drug release:

Source	Sum of squares	D f	Mean squares	F value	p-value Prob>F
Model	468.73	6	78.12	4.98	0.3301
X_1	3.65	1	3.65	0.2325	0.7140
X_2	64.98	1	64.98	4.14	0.2907
X_3	345.84	1	345.84	22.06	0.1336
X_2X_3	36.98	1	36.98	2.36	0.3675
X_1X_2	9.68	1	9.68	0.617	0.5760

Figure-2: Dissolution rate:

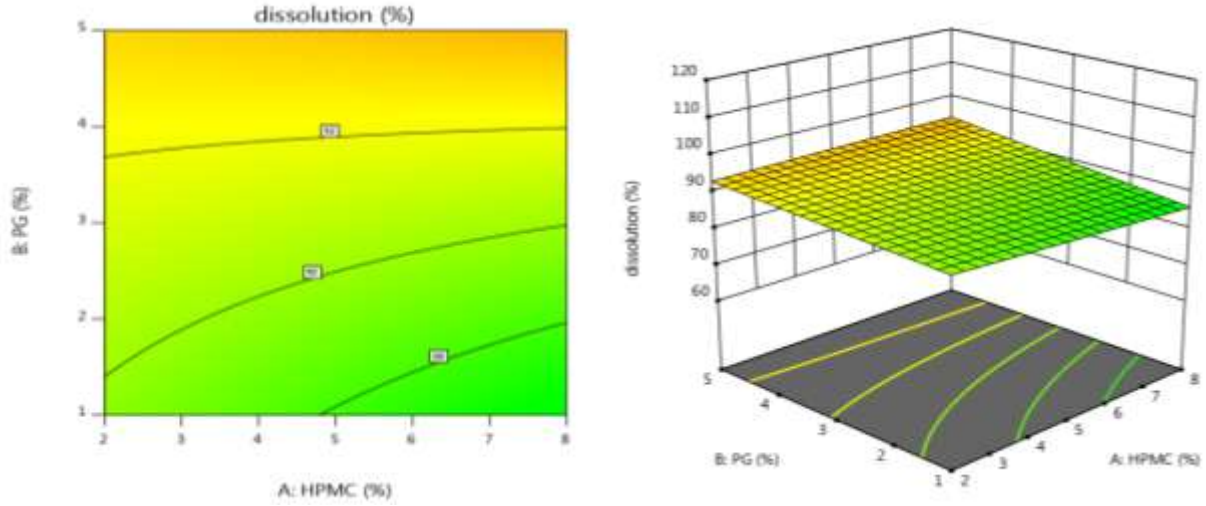


Fig-2: Contour plot showing Effect of HPMC on DR of film

Response 3: Effect on folding endurance: Themodel purpose the following polynomial equation for the folding endurance**.**

Folding endurance (Y_3) = + 271.37500 + 0.625000 * HPMC + 0.458333 * PG - 13.25000 * SSG + 0.208333 * HPMC * PG +2.25000PG*SSG.

Where, Y3 is folding endurance, X_1 is the concentration of polymer, X_2 is the concentration of plasticizer and X_3 is the concentration of superdisintegrant. The model F-value0.0124 indicates the model is significant ($p<0.05$). A positive value in above equation represents the synergic effect of the independent variable and a negative value represents the antagonistic effect.

Table-5: Response 3: Effect on folding endurance

Source	Sum of squares	D f	Mean squares	F value	p-value Prob>F
Model	6062.50	5	1212.50	7.46	0.1224
X_1	112.50	1	112.50	0.6923	0.4929
X_2	2812.50	1	2812.50	17.31	0.0532
X_3	2112.50	1	2112.50	13.00	0.0691
X_1X_2	12.50	1	12.50	0.0769	0.8075
X_2X_3	1012.50	1	1012.50	6.23	0.1299

Figure-3: Folding endurance:

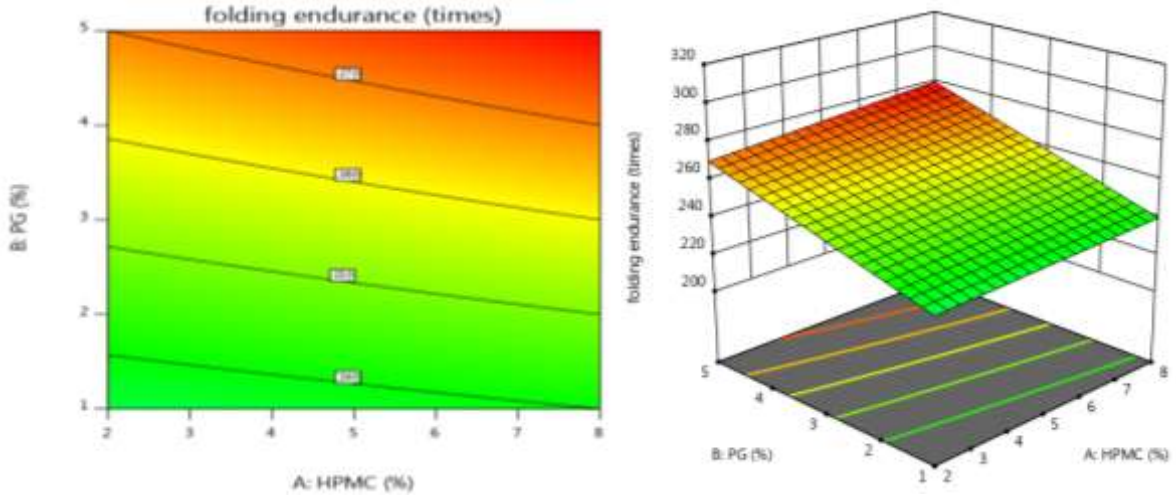


Fig-3: Contour plot showing Effect of HPMC on FE of film

Table-6: Optimized Formulation (F9):

F9 Formulation	**Percentage of Ingredients**	**Predicted Responses**	**Practical Responses**
HPMC(X_1)	4	11	10
Propylene glycol (X_2)	1.5	90.72	93.15
Sodium starch glycolate(X_3)	4	256.25	260

Conclusion:

Oral fast dissolving films were prepared by HPMC E5 as a polymer, propylene glycol as a plasticizer, sodium starch glycolate as a super disintegrant and aspartame as sweetener. Optimization was done by using 2^3 factorial design. The optimized batch was prepared by using 4% of HPMC E5, 1.5 % of propylene glycol and 4% of sodium starch glycolate. It gave disintegration time of 10sec, drug release of 93.15% and folding endurance of 260 times. From the above research work it is concluded that oral fast dissolving film of zolmitriptan was successfully designed and developed by solvent casting method and it gives quick onset of action, improves patient compliance.

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