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FORMULATION AND OPTIMIZATION OF RIZATRIPTAN BENZOATE ORAL FAST DISINTEGRATING FILMS

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ABSTRACT
The aim of present research work was to develop and optimize oral fast disintegrating film of rizatriptan benzoate to improve bioavailability and patient compliance. Rizatriptan benzoate is a serotonin 5-HT1 receptor agonist. It is a new generation anti-migraine drug which has oral bioavailability of 45% due to hepatic metabolism. Oral fast disintegrating films of rizatriptan benzoate 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 was added as sweetener. The physical mixture of drug and polymer characterised by FTIR showed compatibility. A 2^3 factorial design was employed for the optimization of developed formulation considering concentration of polymer, plasticizer and superdisintegrant as independent variables with drug release, disintegration time, folding endurance as dependent variables. 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% HPMC E5,1.5% of propylene glycol and 4% of sodium starch glycolate showed disintegration time 8 sec, drug release 99.15% and folding endurance of 264 times. The stability study result reveals that there was no significant change in paraeters after three months. From the above research work it is concluded that oral fast disintegrating film of rizatriptan benzoate was successfully designed and developed by solvent casting method and it gives quick onset of action, patient compliance.

KEYWORDS: Rizatriptan benzoate, hydroxyl propyl methyl cellulose, propylene glycol, sodium starch glycolate.

INTRODUCTION
The oral route is the most acceptable drug delivery route from patient compliance aspects. Tablets and capsules are the most commonly used solid dosage forms. Among that one of such new dosage form is oral film that rapidly disintegrates and dissolves on the tongue. Recently oral film has started gaining in popularity and acceptance for the reason of rapid disintegration and self administration without water or chewing. Fast disintegrating films are generally constituted of plasticized hydrocolloids or blends made of thereof that can be laminated by solvent casting or hot melt extrusion.[1,2]

Patients who have difficulty in swallowing such as elder persons, pediatric patients and other suffering from mental illness and developmental disorders can be treated with oral films. The buccal mucosa being vascularised, drugs can absorb directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism.[2] The critical parameters to formulate a fast dissolving film are choice of polymer and excipients like superdisintegrant and optimization of concentration of polymer, plasticizer as well as superdisintegrant. The main criteria of fast dissolving films are to disintegrate rapidly on tongue and give rapid onset of action. Several classes of drugs can be formulated as mouth dissolving films including antimigarines, antitussives, antiulcers, expectorants and NSAIDS.[3,4]

Migraine is a chronic neurological disorder characterized by recurrent moderate to serve headaches often in association with a number of autonomic nervous system symptoms. Approximately 20% of the population is affected by migraines in some point of life. Typically the headache affects one half of the head, is pulsating in nature, and lasting from 2 to 72 hours. Associated symptoms may include nausea, vomiting, sensitivity to light, sound, smell. The pain is frequently accompanied by nausea, vomiting, sensitivity to sound, fatigue and irritability. In a basilar migraine, a migraine with neurological symptoms related to the brain stem or with neurological symptoms on both sides of the body, common effects include light-headedness, and confusion.

Nausea occurs in almost 90% of people and vomiting occurs in about one third.[5]

Rizatriptan benzoate is a new generation anti migraine drug, an orally active serotonin 5-HT1 receptor agonist that potently bind to 5HT1B/1D sub types. Rizatriptan Benzoate is freely soluble in water and saliva. The drug having the rapid absorption but the bioavailability is 45% due to its first pass effect, the half life of the drug was around 2-3 hours. It is available in conventional tablet form, so the onset of action is slow. So there is a need to formulate a dosage form which gives fast relief from headache and at the same time it should minimize the first pass effect so that it improves the bioavailability. Fast disintegrating film is the recently developed technology which offers fast, accurate dosing in a safe manner, without the need of water or measuring devices, it improves the patient convenience.[5]

EXPERIMENTAL WORK

Materials

Rizatriptan Benzoate was obtained as gift sample from Porus laboratories, Hyderabad. HPMC E 5 was obtained from Mylan labs, Hyderabad. Propylene glycol was obtained from Reachem, Mumbai. Aspartame and Sodium starch gylcolate was obtained from Dr. Reddy's laboratories, Hyderabad.

METHODOLOGY

Preparation of fast disintegrating films

Fast disintegrating films of rizatriptan benzoate was prepared by solvent-casting evaporation method. The composition of the formulation is presented in table 9. The required quantity of polymer (HPMC) and plasticizer (propylene glycol) was dissolved n double distilled water. This polymeric dispersion was stirred for 1 hr using magnetic stirrer and kept aside to remove all air bubbles entrapped. In another beaker the aqueous solution was prepared by dissolving specified quantities of drug (rizatriptan benzoate), super disintegrant (sodium starch glycolate), aspartame in specific proportion in the mixture of distilled water. The resulting aqueous solution was added to polymeric dispersion and stirred for 1 hr. After removal of air bubbles, the polymeric solution containing drug was casted on the film former (VJ instruments, Mumbai) and temperature was maintained at 30-50ºC. Dried film was carefully removed from film former and trimmed into 3×3 cm^2 size. Trimmed films were stored in air tight container and subjected for evaluation studies.

2^3 factorial design for formulation of films

Statistical analysis of the experimental work was carried out using Design Expert 10 portable software. 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) were selected as independent variables while disintegration time (Y_1), *In vitro* drug release (Y_2), folding endurance (Y_3) were selected as dependent variables.

Table 1: Independent Variables and Their Levels.

Variables	Low level (-1)	High level (+1)
A = amount of HPMC E 5 (%)	4	6
B = amount of PG (ml)	1	3
C = amount of SSG (%)	2	4

Table 2: Full Factorial Design Layout.

Formulation code	Variable levels		
	X_1 (Polymer)	X_2 (Plasticizer)	X_3 (Superdisintegrant)
F1	-1	-1	-1
F2	-1	-1	+1
F3	+1	+1	-1
F4	+1	-1	-1
F5	+1	-1	+1
F6	-1	+1	+1
F7	+1	+1	+1
F8	-1	+1	-1

Table 3: Factorial Batches Composition.

S. No	Ingredients	Formulation codes							
		F1	F2	F3	F4	F5	F6	F7	F8
1	Rizatriptan benzoate(mg)	116	116	116	116	116	116	116	116
2	HPMC E 5 (%)	4	4	6	6	6	4	6	4
3	Propylene glycol (ml)	1	1	3	1	1	3	3	3
4	Sodium starch glycol ate (%)	2	4	2	2	4	4	4	2
5	Aspartame (mg)	25	25	25	25	25	25	25	25
6	Water (ml)	10	10	10	10	10	10	10	10

EVALUATION OF ORAL FAST DISINTEGRATING FILMS

a) FTIR studies

As a part of the Preformulation studies, drug-polymer interaction study was performed by using Fourier Transform Infrared Spectroscopy (FTIR). The FTIR spectra of rizatriptan benzoate, HPMC E5, Formulation and their physical mixture were recorded individually.[9] The samples were scanned in the range of 400-4000cm^{-1}.

b) Morphological Properties

Morphological properties such as the homogenous nature of film, colour, transparency and surface of films are tested visually. All the formulations were stored at room temperature (25± 1^oC) in air tight containers.[5]

c) Uniformity of film Thickness

Thickness was measured by using micrometer screw gauge at 5 different strategic locations on the film. This helps in determining the uniformity of thickness of oral fast disintegrating films which directly relates to the accuracy of the dose.[6]

d) Folding endurance

Folding endurance proved the information regarding the flexibility as well as the physical ability of the films. It was measured by firmly folding films repeatedly at the middle. The number of folds on the same place, required to produce crack in the film was noted as the value of folding endurance.[6]

e) *In vitro* disintegration time

Petri dish method

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 films were carefully placed at the centre of the Petri dish. The time taken by the film to disintegrate is measured and the test is performed in triplicate manner.[6,7]

f) Surface pH

The films 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. The surface pH of the films were 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 and values were compared by using bar chart.[7]

g) Drug content uniformity

Three films 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 films gets dissolved. All the solutions were filtered and samples were analysed by using Double beam UV spectrophotometer used plain placebo solution as blank. An average of the 3 trails was taken as drug content in each film. The same procedure was repeated for the remaining formulations.[7,8]

h) *In vitro* dissolution studies

In vitro 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^oC. 2×2cm^2 films were 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 using borosil quantitative grade 1 what man filter paper and diluted suitably and analysed by using a UV spectrophotometer at 226nm by blank correction method. Dissolution of each formulation was performed in triplicate manner and average value of 3 trials were taken and used to calculate the drug release profile.[8]

i) Tensile strength

Three films from each formulation were took and cut in to 5 cm width and 10 cm length. Breaking force of each film was determined using Tensile strength apparatus (H1KS Tensile strength apparatus HTE-500N) and the mean and standard deviation were calculated using the formula.[9]

Tensile strength = Breaking force / Area of cross section

j) Percentage Elongation

Percentage elongation provides the information regarding mechanical property of the films. When the physical force is applied on the film it stretches and it is referred as strain. Strain refers the deformation of film divided by the original dimension of the film. Percentage elongation increases with an increase in the plasticizer concentration. It was calculated by using following formula.[9]

$$Percentage\ elongation = (L\text{-}L_o) / L_o \times 100$$

Where, L = final length, L_o = initial length

k) Stability studies

The optimized formulation will be evaluated for stability studies by storing it at 40^0C and 75%RH for 3 months and analysed for physical appearance, disintegration time, drug content and *in-vitro* release rate.[9]

RESULTS

Drug Excipients Compatibility Studies

Infra-red Studies

IR spectrum of Rizatriptan benzoate, HPMC E 5 and physical mixture was recorded, and it was in accordance with the reported peaks. It is shown in Following Figure.no.3. The IR spectra of Rizatriptan benzoate comply with its chemical structure and show peaks for principle group's. The structural assignments for the characteristics absorption bands are listed in Following Table no.4.

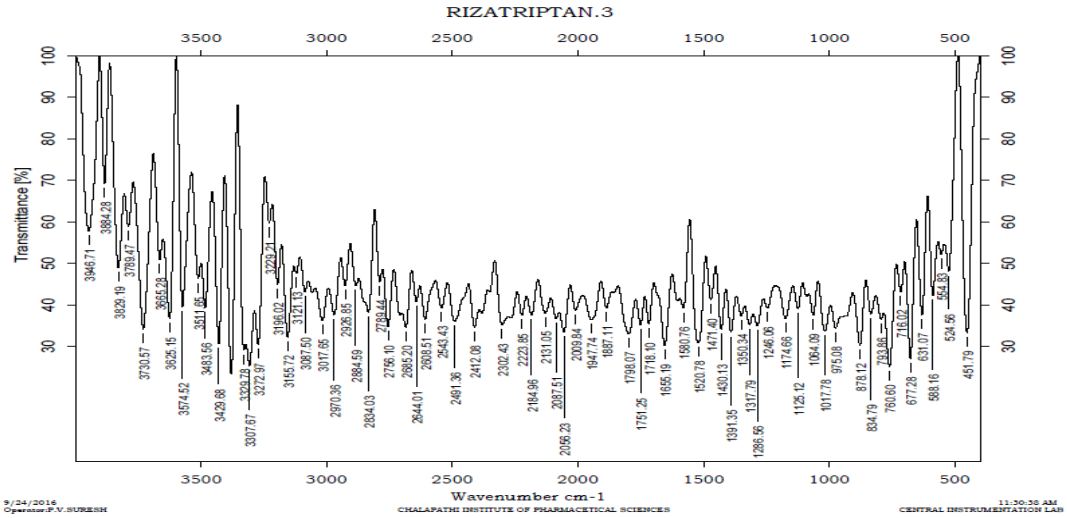

Fig. 1: FTIR spectra of Rizatriptan Pure Drug.

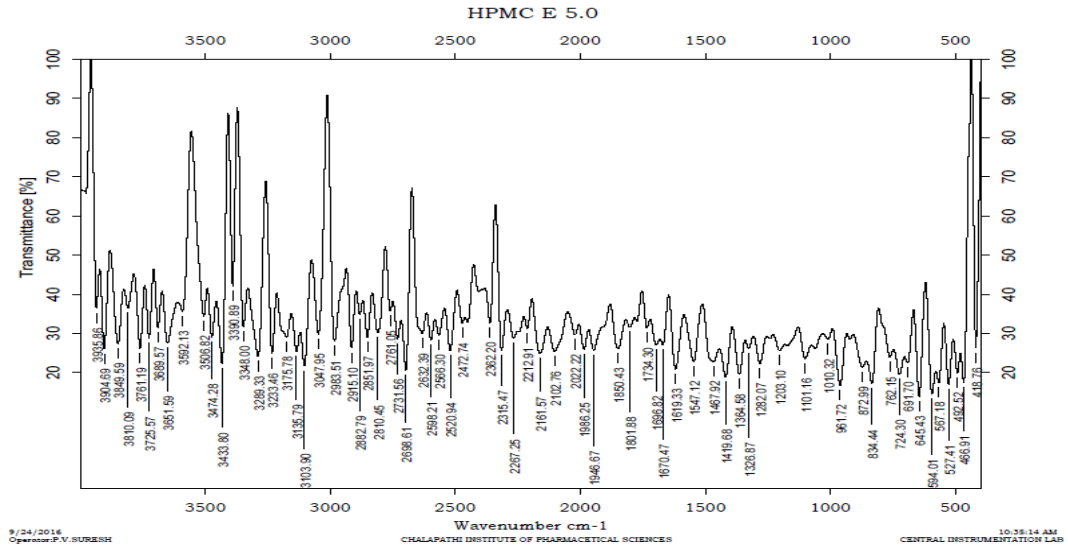

Fig. 2: FTIR spectra of HPMC E 5.

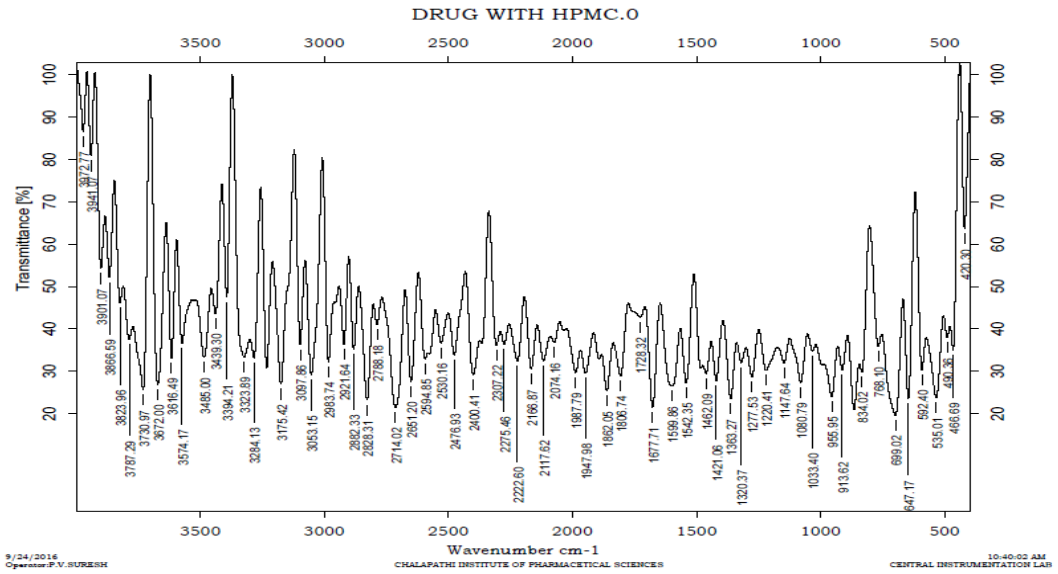

Fig. 3: FTIR spectra of physical mixture of drug with polymer (HPMC).

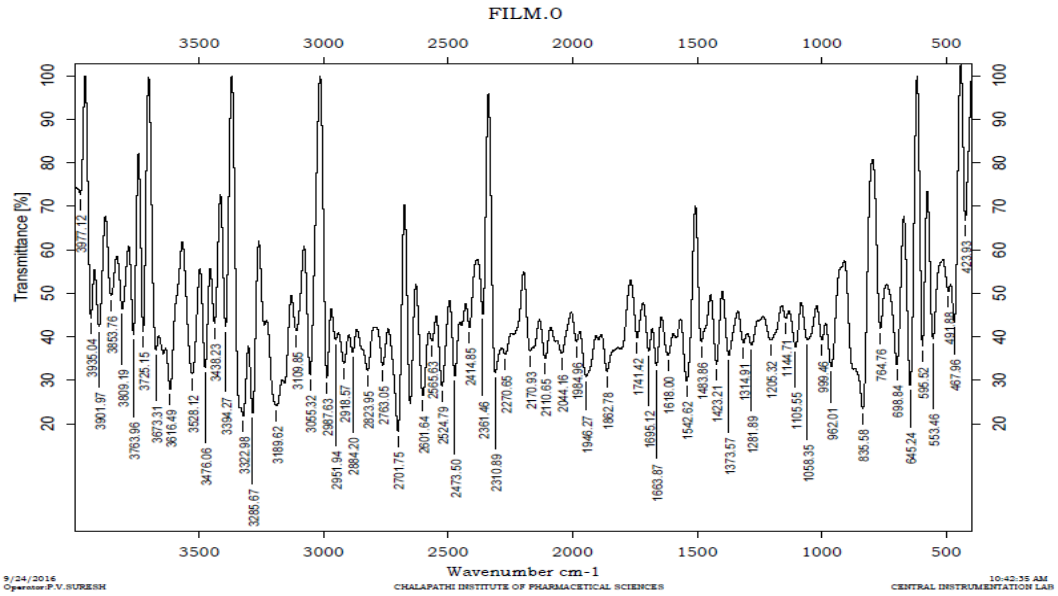

Fig. 4: FTIR spectra of Rizatriptan Film.

Table 4: Infrared Spectral assignment for Rizatriptan benzoate.

Type	Pure drug	Formulation
N-H Stretching	3446	3478
CH_3 Stretching	2947	3003
CH_2 Stretching	2893	2897
C=C Stretching	1608	1625

Physical Characteristics of Films

Rizatriptan benzoate fast disintegrating films were prepared by solvent casting evaporation technique were transparent, smooth, soft and colourless in nature. Drug content uniformity was in the range of 93.22 to 99.81% while the thickness of the film was in the range of 0.020 to 0.291mm. Folding endurance of the film ranged from 230 to 264 and pH of the film was 6.53 to 6.80. Tensile strength was in the range of 1.27 to 2.41kg/mm^2 and percentage elongation ranges from 21.5 to 33%. Disintegration time was in the range of 8 to 16 sec. All the Physical parameters are summarized in table 4.

Table 5: Evaluation of Physico- mechanical properties of films.

Batches	Film Nature	Thickness (mm)	Tensile strength (kg/mm^2)	% Elongation
F1	Transparent	0.020 ± 0.002	1.27±0.02	12.5±0.04
F2	Smooth	0.148 ± 0.004	1.48±0.02	23.3±0.04
F3	Smooth	0.199 ± 0.004	1.8±0.03	28.6±0.06
F4	Transparent	0.283 ± 0.003	2.3±0.01	30.6±0.03
F5	Smooth	0.012 ± 0.003	1.31±0.02	16.6±0.06
F6	Transparent	0.145 ± 0.005	1.50±0.03	23.3±0.05
F7	Transparent	0.205 ± 0.005	1.86±0.03	26.6±0.08
F8	Smooth	0.291 ± 0.001	2.41±0.01	33.0±0.05

Table 6: Evaluation of Physico- mechanical properties of films.

Batches	Surface pH	Folding endurance	Drug content (%)	Disintegration time (sec)
F1	6.67 ± 0.062	230	96.36 ± 2.46	10± 0.04
F2	6.80 ± 0.026	239	99.10 ± 1.64	09 ±0.24
F3	6.80 ± 0.026	260	97.60 ± 1.28	16 ± 0.03
F4	6.76 ± 0.023	251	93.22 ± 1.44	13 ± 0.28
F5	6.65 ± 0.030	257	95.65 ± 0.42	12 ± 0.24
F6	6.80 ± 0.020	264	99.81 ± 1.09	08 ± 0.01
F7	6.53 ± 0.030	247	98.75 ± 0.78	16 ± 0.03
F8	6.66 ± 0.030	243	97.45 ± 0.91	11 ± 0.10

Table 7: Dissolution Study.

Time	F1	F2	F3	F4	F5	F6	F7	F8
0 min	0%	0%	0%	0%	0%	0%	0%	0%
1 min	55.67%	48.56%	36.25%	47.61%	40.12%	59.65%	34.95%	47.21%
2 min	69.89%	52.35%	44.32%	60.68%	49.23%	72.24%	41.58%	58.29%
3 min	75.09%	64.26%	53.56%	72.24%	55.23%	85.00%	52.63%	72.52%
4 min	82.67%	78.25%	61.23%	84.62%	69.25%	90.47%	65.23%	81.24%
5 min	86.76%	88.16%	87.325	91.63%	80.19%	95.84%	84.18%	90.17%

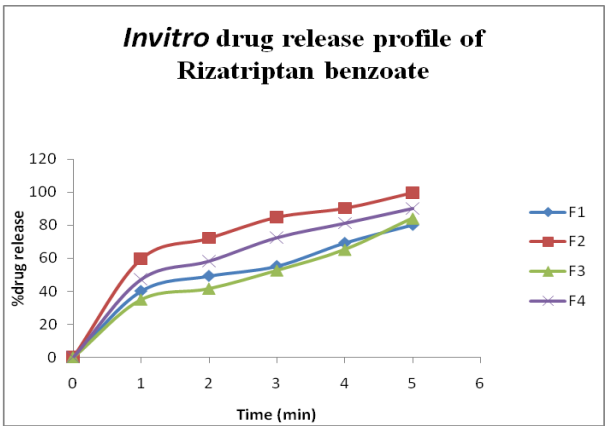

Fig. 5: *In-vitro* drug release profile of Rizatriptan benzoate (F1-F4).

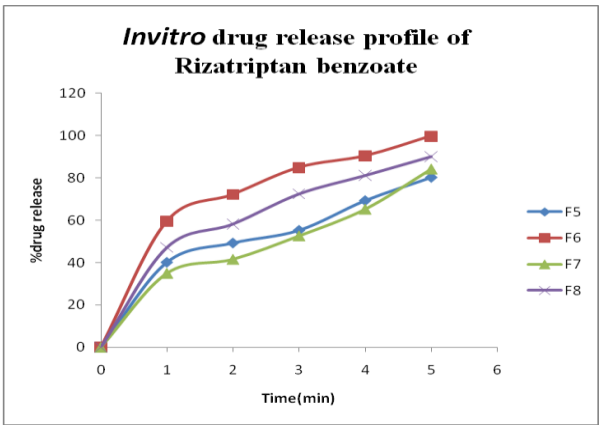

Fig. 6: In-vitro drug release profile of Rizatriptan benzoate (F5-F8).

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 8-16sec, 84.18-99.84% and 230-268 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 (Y1): effect on disintegration time

The model purpose the following polynomial equation for disintegration time.

Y1 = +91.44 -2.24A-2.75B +1.77C+0.75AC

Where, Y1 is disintegration time, A is the concentration of polymer, B is the concentration of plasticizer and C is the concentration of superdisintegrant. The model F-value 0.0160 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 8: Analysis of variance for response Y1.

Source	Sum of squares	D f	Mean squares	F value	p-value Prob>F	Significance
Model	2331	4	582.75	20.69	0.0160	S
A	84.50	1	84.50	3.00	0.0045	S
B	224.50	1	224.50	79.69	0.0030	S
C	2.00	1	2.00	0.071	0.0035	S
AC	11.22	1	11.22	1.50	1.00	-

Response 2 (Y2): effect on drug release

The model purpose the following polynomial equation for drug release

Y2 = +11.88-1.63A+2.12B+0.12C-0.62BC

Where, Y2 is drug release, A is the concentration of polymer, B is the concentration of plasticizer and C is the concentration of superdisintegrant. The model F-value 0.0179 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 9: Analysis variance for response Y2.

Source	Sum of squares	D f	Mean squares	F value	p-value Prob>F	Significance
Model	60.50	4	15.13	19.11	0.0179	S
A	21.13	1	21.13	26.68	0.0141	S
B	36.12	1	36.12	45.63	0.0066	S
C	0.13	1	0.13	0.16	0.7117	S
BC	3.13	1	3.13	3.95	0.1411	-

Response 3 (Y3): effect on folding endurance

The model purpose the following polynomial equation for the folding endurance

Y3 = +249.88-4.88A+6.62B+0.87C-4.62AB

Where, Y3 is folding endurance, A is the concentration of polymer, B is the concentration of plasticizer and C is the concentration of superdisintegrant. The model F-value0.0300 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 10: Analysis variance for response Y3.

Source	Sum of squares	D f	Mean squares	F value	p-value Prob>F	Significance
Model	699.50	4	233.17	6.66	0.0300	S
A	540.03	1	540.03	1.39	0.2838	S
B	48.29	1	48.29	11.93	0.0136	S
C	18.24	1	18.24	2.91	0.0286	S
AB	183.0	1	183.0	2.80	0.1930	-

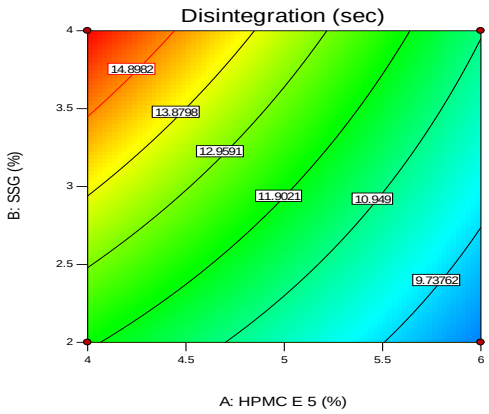

Fig. 7: Contour plot showing effect of HPMC on DT of film.

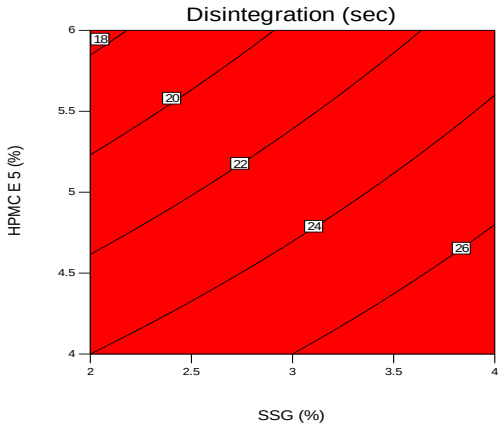

Fig. 8: Contour plot showing Effect of SSG on DT of film.

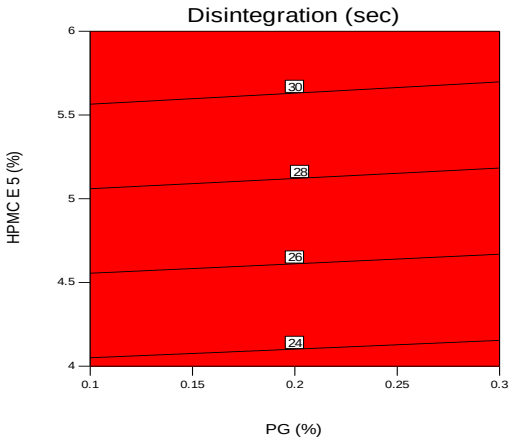

Fig. 9: Contour plot showing Effect of PG on DT of film.

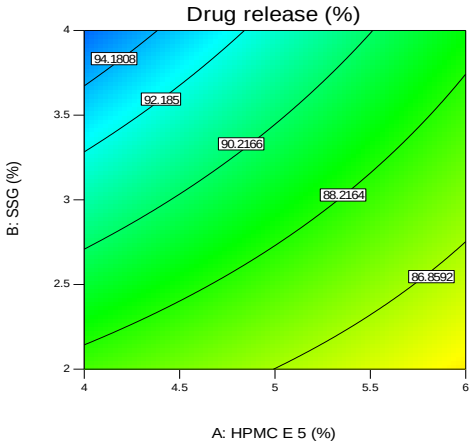

Fig. 10: Contour plot showing Effect of HPMC on DR of film.

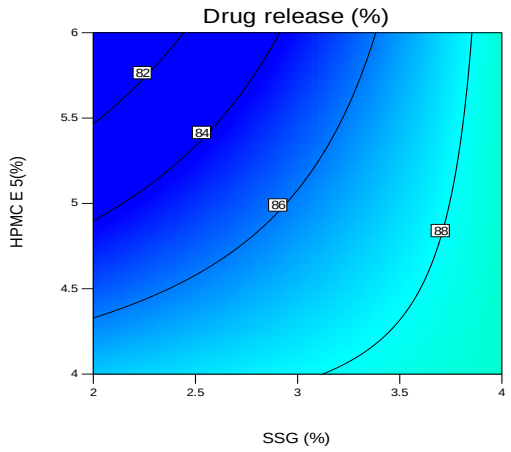

Fig. 11:Contour plot showing Effect of SSG on DR of film.

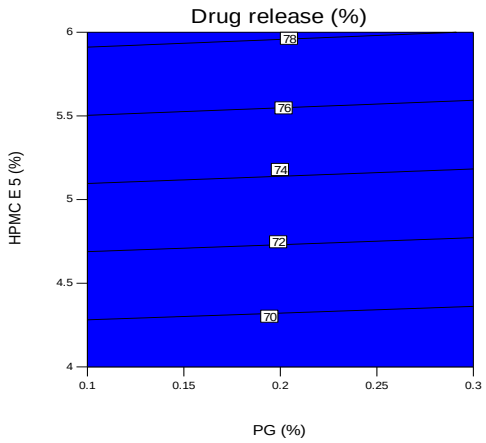

Fig. 12: Contour plot showing Effect of PG on DR of film.

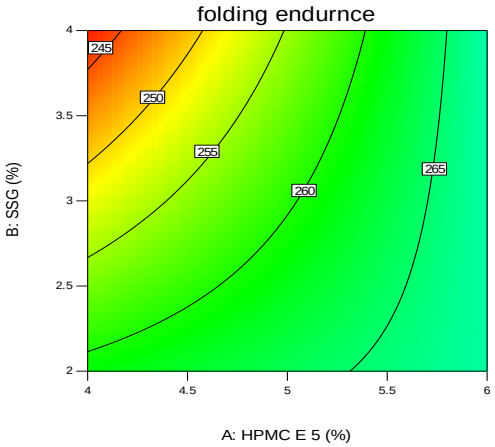

Fig. 13: Contour plot showing Effect of HPMC on FE of film.

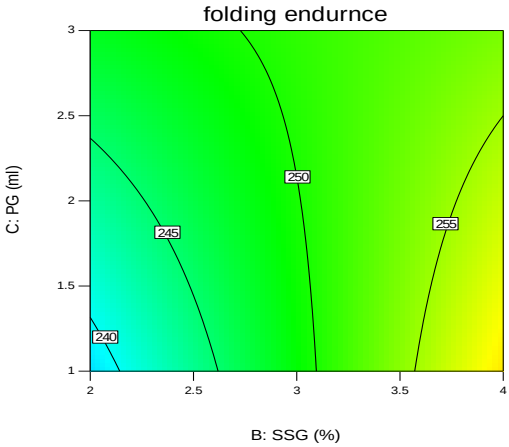

Fig. 14: Contour plot showing effect of SSG on FE of film.

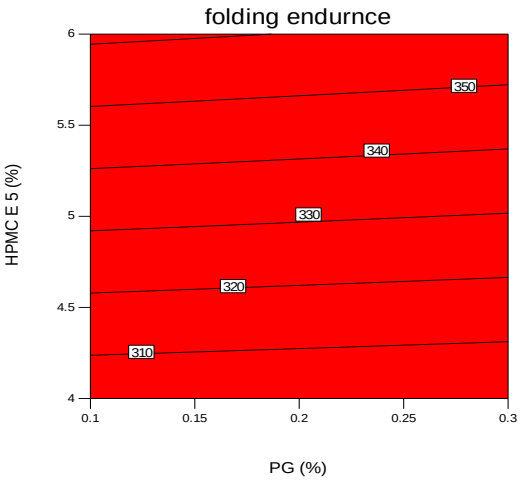

Fig. 15: Contour plot showing Effect of PG on FE of film.

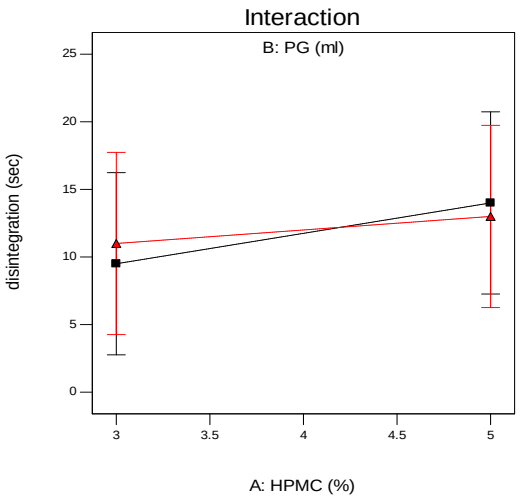

Fig. 16: plot showing the interaction between two factors (A&B).

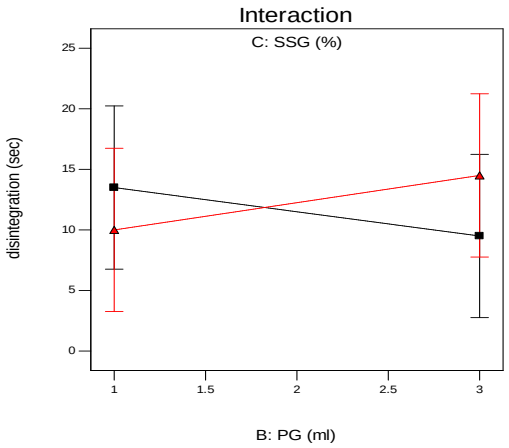

Fig. 17: plot showing interaction between two factors (B&C).

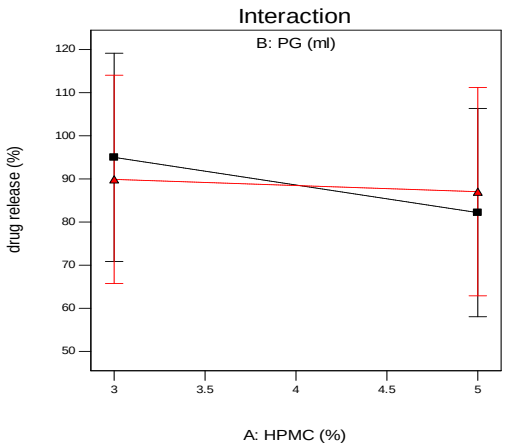

Fig. 18: plot showing interaction between two factors (A&B).

OPTIMIZATION

The formulation of 8 batches of oral films according to 2^3 factorial design was carried out. The formulated batches were evaluated for various physicochemical parameters. All the formulations shows good characteristics but there is a need to optimize the formulation because from the contour plots (7,8 & 9) there is an decrease in disintegration time and drug release due to increase in polymer and plasticizer concentrations because there is an interaction between the factors. The interaction was shown in plots.no. 16, 17 &18.so from the interaction plots it clears that the concentration of polymer is 4% and plasticizer concentration is 1.5%. The optimized formulation contains 4% of polymer, 1.5% of plasticizer and 4% superdisintegrant. The prepared formulation was evaluated for drug release, disintegration time and folding endurance. The results were shown in table. no.10.

Table 11: Results of Optimized Formulation.

S. No	Optimized formulation		
	Disintegration time (sec)	*In Vitro* drug release (%)	Folding endurance
1.	08	99.01%±0.01	264

Stability studies

The optimized formulation was evaluated for stability studies which was stored at 40^0C at 75%RH for 3 month and analysed for physical appearance, disintegration time, drug content and *in-vitro* release rate at 1 month interval. It was found that films retained its physical appearance and there was no much significant change in the values of disintegration time, drug content and *in-vitro* release studies. The results are shown in table no.15. The obtained results indicated that the oral films are stable at 40^0C at 75% RH. Table: 12 Stability data for Optimized Formulation.

S. No	Optimized formulation stored at 40^0C/75%RH		
	Physical appearance	Disintegration time (sec)	Drug content (%)
1	Transparent	8±0.01	99.79±0.01
2	Transparent	7±0.04	99.70±0.05
3	Transparent	7±0.04	99.53±0.01

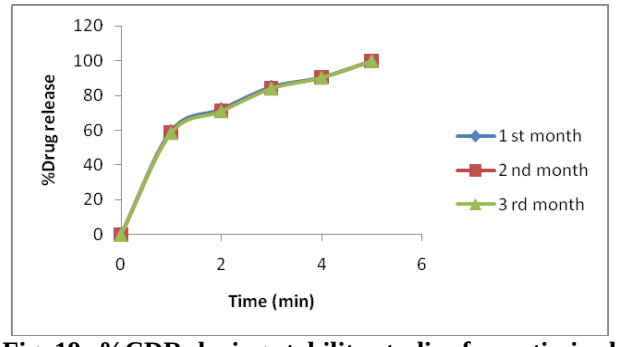

Fig. 19: %CDR during stability studies for optimized formulation.

CONCLUSION

The main aim of the present study was to develop oral fast disintegrating film of rizatriptan benzoate for the treatment of migraine. Oral fast disintegrating 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. From the above research work it is concluded that oral fast disintegrating film of rizatriptan benzoate was successfully designed and developed by solvent casting method and it gives quick onset of action, patient compliance.

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CONFLICT OF INTEREST
Conflict of interest is declared by none.

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