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Research Article

Formulation and Optimization of Fast-Dissolving Film Containing Rizatriptan Benzoate

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ABSTRACT

Fast-dissolving films are developed to overcome difficulty with swallowing which encountered not only in pediatric or geriatric populations but also in the case of handicapped, mentally retarded or bedridden patients. The present study was aimed to formulate fast dissolving film to enhance bioavailability and to avoid first pass effect. The key is to develop successful fast dissolving film by solvent casting method and select right compatible excipients using FTIR and DSC study. The present study describes formulation, optimization and evaluation of fast dissolving film of rizatriptan benzoate in which physical and mechanical parameter such as appearance, thickness, folding endurance, surface pH, disintegration time, in-vitro drug release was evaluated. The formulation was optimized by Box-Behnken design using Design Expert software. The effect of film-forming polymer composition and plasticizer concentration on disintegration time and in-vitro drug release behavior were investigated. The F8 batch was an optimized formulation with less disintegration time of 09 seconds and high in-vitro drug release of 99.58%.

Keywords: Fast Dissolving Film, Rizatriptan Benzoate, Migraine formulation, oral film.

INTRODUCTION

Among other routes oral route is the most preferred route for drug administration due to its ease of administration, acceptability, adaptability, non-invasiveness, and patient compliance[1]. Fast dissolving drug delivery system developed in the late 1970s as a substitute for traditional dosage forms i. e. tablets and capsules. Fast dissolving film is a stamp size thin film embedded with drug molecules and other additives which rapidly hydrate and dissolve within seconds to minutes when placed in the oral cavity with or without water for oromucosal and intragastric absorption[2-6]. FDF mainly comprises of hydrophilic polymer due to its readily soluble nature and plasticizer to increase plasticity of film and also to reduce glass transition temperature[7-9].

Fast dissolving film are gaining more interest as an alternative to fast dissolving tablets because of fear of choking called dysphagia. Dysphagia is experienced by wide range of age groups 40% of 65 or older, 66% of 16-24, and 35% of both age groups complained that tablets or Capsule were too large to swallow. To overcome this FDDDS (Fast dissolving drug delivery system) was developed. FDF (Fast dissolving film) and FDT (Fast disintegrating tablet) are example of FDDDS. However, FDT developed for disintegration in mouth although fear of choking remains the same, while FDF overcomes the problem of swallowing difficulties and improve patient compliance. This fast-dissolving film follows oromucosal absorption which prevent drug degradation in gastrointestinal tract, first pass metabolism and allows fast and direct access to the systemic circulation.

Research and development on oral drug delivery has led to advancement of solid oral dosage form from simple to modified release tablet/capsule to fast disintegrating tablet to fast dissolving film[10]. However fast dissolving film should not be misapprehended with buccal films developed for staying longer on oral mucosa[11].

MATERIALS AND METHODS

Method of Preparation for Fast Dissolving Film:

Solvent Casting Method

In this method hydrophilic polymer soaked with water for overnight and depending upon drug suitable solvent selected. Both the polymeric solution and drug solution added with other excipients to form homogeneous solution using magnetic stirrer. Air entrapped during mixing removed by a sonicator to form bubble free solution. Then the solution casted on Petri plate and dried at room temperature for 24 hrs. Finally, film from petri plate removed by pilling and cut in desired size and shape[12-14].

Procedure for preparation of fast dissolving film:

Weighed accurate amount of polymer and soaked in 10 ml of water in 50 ml beaker for overnight. Required amount of Rizatriptan Benzoate dissolve in 10 ml water in 50 ml beaker. Then in the polymeric solution plasticizer was added and stirred for 30 minutes. In the beaker containing drug solution other excipients added step by step like citricacid, aspartame, etc. Then drug solution containing excipients added to the polymeric solution withcontinuous stirring. The solution mixture stirred for 1 hr and then sonicate for 30 minutes to remove airbubble from solution. Then the resulting solution was casted on petri plate (Area of 63.58 cm^2) and dry at room temperature for 24 hrs. The funnel was placed on petri

plate for even drying of surface of the film. Finally, the film was cut in to size of 2×2cm^2 containing 10 mg of RizatriptanBenzoate. After this the prepared film were stored in aluminum foil in plastic zip lock pouch containing small silica bags to avoid moisture. 115.50 mg dose of Rizatriptan Benzoate was taken after calculating dose[15-17].

Dose Calculation:

The drug to be loaded in film was determined by dose calculation by calculating the area of peri plate. The dose calculated by following method.

Rizatriptan 269.40 mg ≅ Rizatriptan Benzoate 391.46 mg

Dose of Rizatriptan Benzoate is 5 mg

So, $5mg = 5 \times \frac{391.46}{269.40} = 7.265\ mg$

Area of petri plate = π r²

Radius of petri plate= 4.5 cm

π r²= 3.14×4.5×4.5

Area of petri plate= π r²=63.58 cm^2

Area of film= 2×2=4 cm^2

For each film 4 cm^2 contain 7.265 mg of rizatriptan benzoate

In petri plate of area 63.58 cm^2 contain = $63.58 \times \frac{7.265}{4} = 115.50$ mg

CHARACTERIZATION OF DRUG AND POLYMER

Melting Point

The melting point was determined by introducing small amount of drug in capillary which put in melting point meter and constant heat was applied with electrical coil. The temperature at which the drug melted was noted as melting point. The melting point observed was 178-180 °C.

Determination of λ max

Accurately weighted 10 mg of Rizatriptan benzoate was transferred into 100 ml volumetric flask and volume was made up to 100 ml with phosphate buffer of pH 6.8. From this solution, 1 ml withdrawn and added to 10 ml volumetric flask and diluted up to 10 ml with phosphate buffer of pH 6.8. Finally, the sample was scanned in the 200-400 nm range. The wavelength of the maximum absorption λmax was found to be 225.91 nm.

Differential scanning calorimetry

The DSC was carried out for obtained sample of Rizatriptan benzoate to confirm its purity. The DSC pattern were recorded on Lab Mettler System when the drug was heated in crimped

aluminum pans at a scanning rate 10 °C per minute using range 40-300 °C (Figure 2).

COMPATIBILITY STUDY OF DRUG WITH POLYMER

FTIR Spectroscopy of Rizatriptan Benzoate with polymer

Rizatriptan Benzoate: Pullulan mixture and Rizatriptan Benzoate: Maltodextrin mixture subjected for IR spectroscopic analysis to ascertain whether there is any interaction between the drug and polymer used. The instrument scans were collected with resolution of 4 cm-1 over the region 4000-500 cm-1. The IR spectra obtained was shown in figure 7 and 8. The IR spectra of drug and physical mixture showed similar characteristic functional peaks. This similarity in peaks indicates the compatibility of Rizatriptan Benzoate with the film forming polymers. Rizatriptan benzoate was found to be compatible with Pullulan and Maltodextrin (Figure 1).

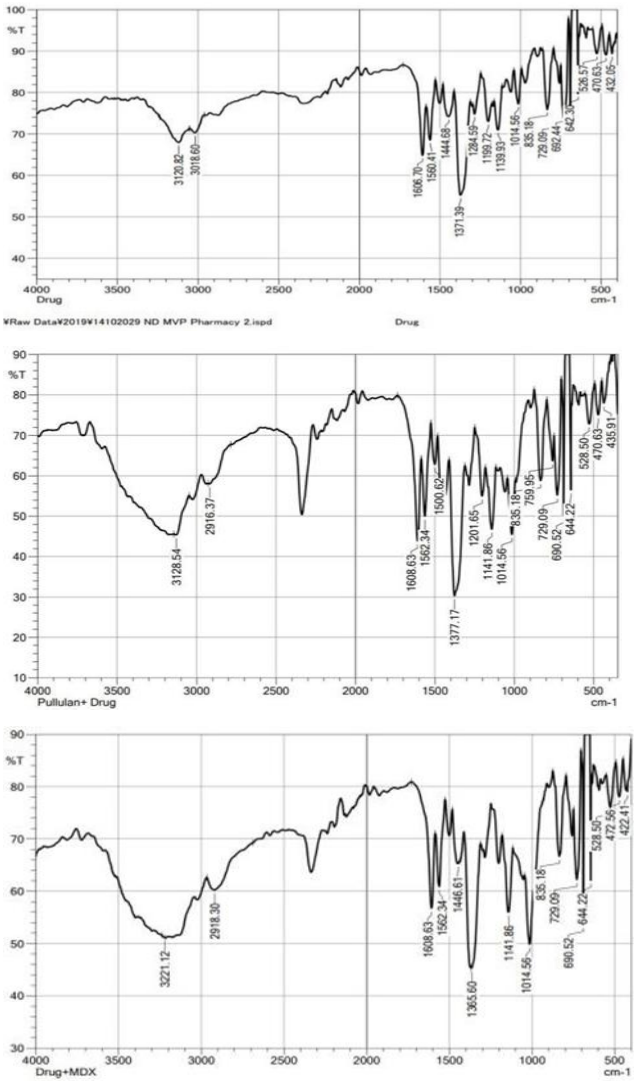

Figure 1: FTIR Spectra of Rizatriptan Benzoate, Pullulan: Drug physical mixture and Maltodextrin: Drug physical mixture

Differential scanning Colorimetry (DSC) study

The DSC thermogram was obtained for pure Rizatriptan benzoate and physical mixture of Rizatriptan Benzoate, Pullulan, and Maltodextrin physical mixture. The DSC patterns were recorded on a Lab Mettler. The physical

mixture of sample was heated in crimped aluminum pans at a scanning rate 10 °C per minute using range 25-300 °C. The DSC thermogram of Drug and Polymer physical mixture are shown in figure 5.

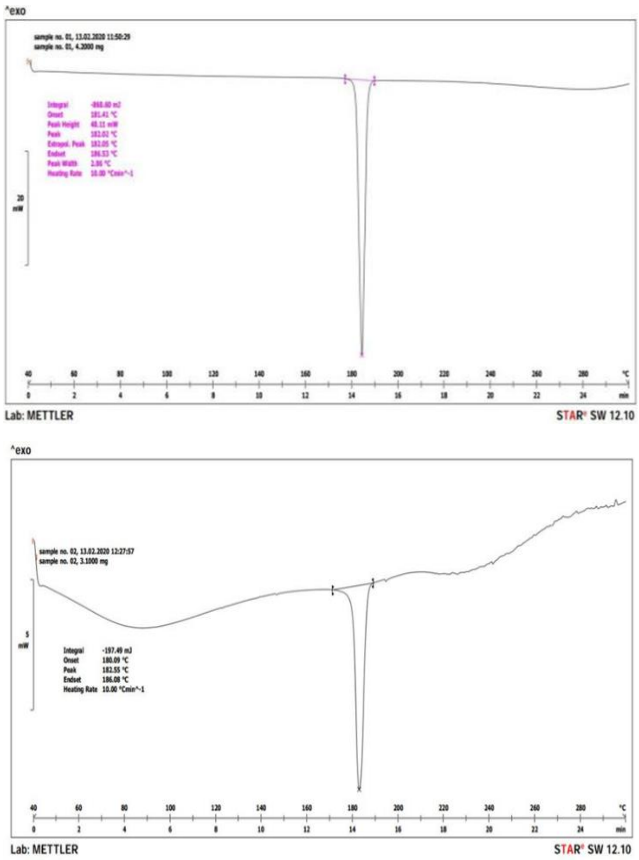

Figure 2: DSC thermogram of Drug and Drug Polymer physical mixture

On the basis of Infrared spectroscopy and DSC thermogram the Rizatriptan benzoate and film forming polymer Pullulan and Maltodextrin were found to be physically compatible with each other.

Screening of polymer and plasticizer for preparation of film

Screening of polymer

Polymer and plasticizer were weighed and measured correctly and evaluated for film forming capacity and appearance. Polymer soaked in water for overnight and added plasticizer. Then the polymeric solution was stirred for 30 minutes using magnetic stirrer and sonicate for 30 minutes to remove air bubbles. Polymeric solution casted on petri plate and dry for 24 hours at room temperature. Afterward, film was separated from casting surface and evaluated for film forming capacity and appearance. From the result obtained polymer and plasticizer were selected for further study. From the screening of polymer, it observed that Lycoat and Maltodextrin failed to form film. HPMC K4M have good film forming capacity and transparent but texture of film was found to be rough. Pullulan and Pullulan: Maltodextrin combination both form excellent film, but polymer combination have better texture that than pullulan. Hence Pullulan and Maltodextrin combination was selected for further studies[18-19].

Screening of plasticizer

All the formulations were subjected to appearance, disintegration time, and folding endurance evaluation. Formulations prepared using propylene glycol were found to be sticky and have more disintegration time. The polyethylene glycol had good texture, less disintegration time, and good folding endurance. Hence polyethylene glycol (PEG) is used as a plasticizer in further formulation.

Optimization of formulation

Selection of polymer - Pullulan and Maltodextrin each polymer was selected for optimization study. The combination of Pullulan and Maltodextrin has sufficient viscosity, disintegration time, and greater film forming capacity than other polymers.

Table 1: Formulation batches for plasticizer screening

Ingredient	S1	S2	S3	S4	S5	S6
Pullulan	300	300	300	300	300	300
Maltodextrin	100	100	100	100	100	100
PEG (ml)	1	2	3	-	-	-
Propylene glycol (ml)	-	-	-	0.5	1.0	1.5
CCS	15	15	15	15	15	15
SLS	2	2	2	2	2	2
Aspartame	10	10	10	10	10	10
Citric acid	20	20	20	20	20	20
Flavor	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Appearance	Semi-transparent	Semi-transparent	Semi-transparent	Semi-transparent	Sticky Semi-transparent	Sticky Semi-transparent
Disintegration time (sec)	33	35	38	55	65	54
Disintegration time (sec)	307	311	326	389	433	466

Table 2: Box-Behnken Design of experiments

Formulation Characteristic	Pullulan			Maltodextrin			PEG		
Levels	200	300	400	50	100	150	2	3	4
Code	-1	0	+1	-1	0	+1	-1	0	+1

Table 3: Box-Behnken Response Design

Formulations	X_1 Pullulan	X_2 Maltodextrin	X_3 PEG
F1	0	+1	+1
F2	0	0	0
F3	+1	0	+1
F4	0	+1	-1
F5	+1	0	-1
F6	-1	0	-1
F7	0	0	0
F8	-1	-1	0
F9	+1	-1	0
F10	-1	+1	0
F11	0	0	0
F12	0	-1	-1
F13	-1	0	+1
F14	0	0	0
F15	+1	+1	0
F16	0	-1	+1
F17	0	0	0

Box-Behnken design

Box-Behnken design is described for a minimum of three factor. Box-Behnken design aresecond order design based on three level incomplete factorial design. One of the main advantages of Box-Behnken design is that it does not contain combination for which all factors are simultaneously at their highest or lowest level. A Box-Behnken design is an economical alternative to central composite design. It also known as orthogonal balanced incomplete block design, there are available for 3 to 10 factors.Because the design involves study at three levels, the quadratic model is considered to be most appropriate model. A comparison between the Box-Behnken design and other response surface design has demonstrated that Box-Behnken is slightly more efficient than the central composite designbut much more efficient than three level factorial design. The box-Behnken design was used in the present study. In this design 3 factors were selected at 3 levels and experimental trials were performed at all 17 possible combinations. Thickness, in-vitro disintegration time, and in-vitro dissolution were selected as dependent variables. Three independent factors the concentration of Pullulan, Maltodextrin, and PEG having three level were selected and coded as -1, 0, and +1. The data obtained were treated using Design-Expert(Version: 12.0.11.0) software and analysis statistically using analysis of variance (ANOVA). The data were subjected to Contour plot and 3D response service to study the interaction of dependent and independent factors [20-21].

Evaluation parameters

Thickness

The thickness of the film can be measured by micrometer screw gauge at different strategic location i.e. four corner and center. The thickness of film is directly proportional to dose accuracy of film.

Surface pH of film

The pH of film determined by putting formulated film in a petri plate and slightly wet by using distilled water then pH meter electrode bring into contact with surface of film after this the surface pH is noted.

Folding endurance

The folding endurance was determined by repeatedly folding one strip at the same place tillit broke or folded up to 300 times which is considered satisfactory to reveal good film properties. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance.

Drug content uniformity

UV spectrophotometrically drug content was determined by using fast dissolving film of 4 cm^2 in 100 ml of 6.8 phosphate buffer using magnetic stirrer. The drug concentrate was evaluated spectrophotometrically at λmax at 225 nm.

In-vitro disintegration

Currently, there are no official guidelines for determining disintegration time of fast dissolving film. Glass petri plate containing 10 ml of 6.8 pH phosphate buffer to mimic saliva pH added and the time taken by film to disintegrate completely is noted (Table 4)[22-23].

RESULTS AND DISCUSSION

Responses surface graphs of Box-Behnken design

All the Model F-value implies model is significant. P-value less than 0.0500indicate model term are significant.

A] The graph shows that as the concentration of polymer increases the thickness of the filmincreases significantly

B] The graph shows that as the concentration of polymer and plasticizerincreases the disintegration time decreases significantly.

C] The graph shows that as the concentration of Pullulan and PEG increases the %CDR of formulation decreases significantly.

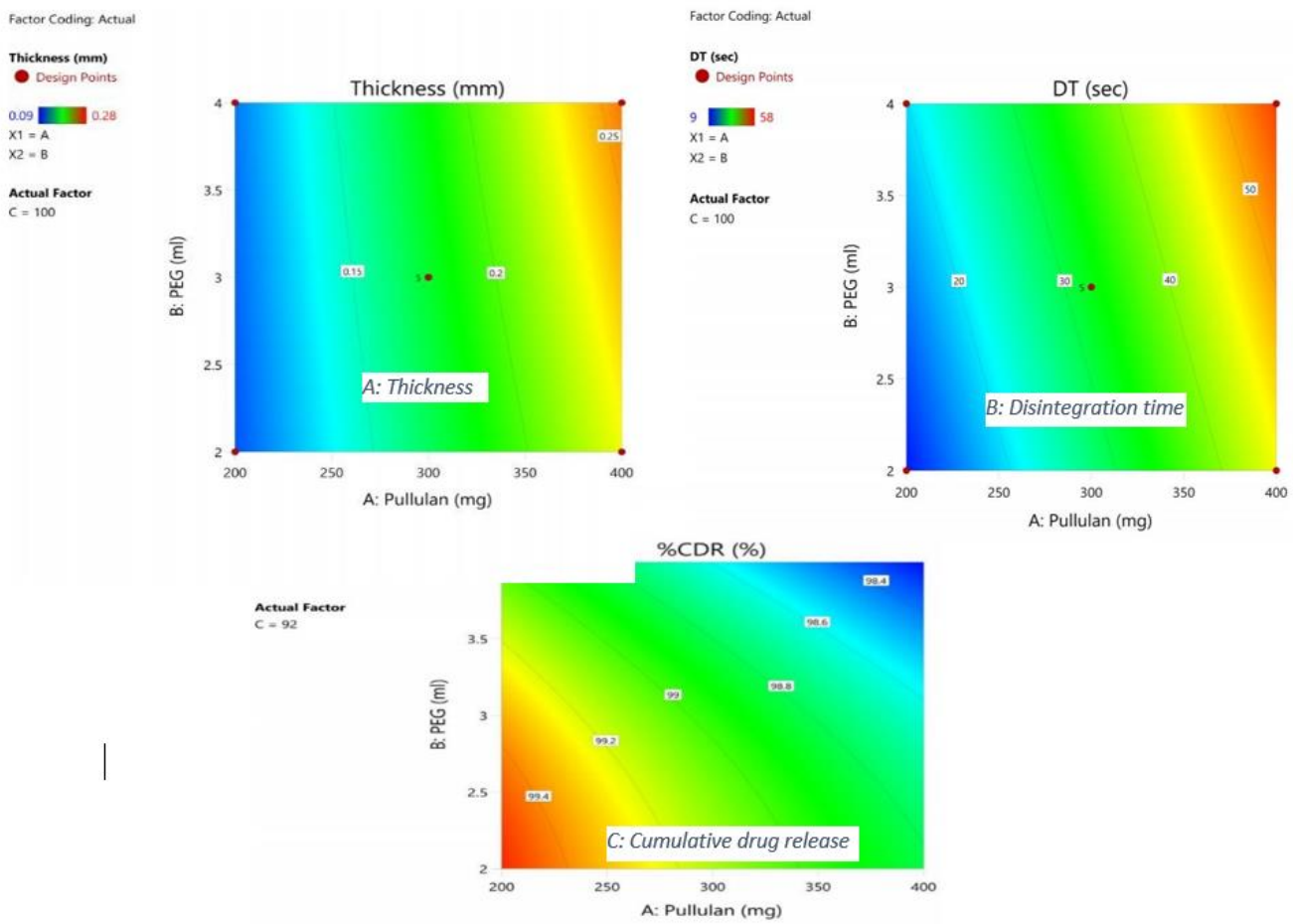

Figure 3: Response surface graph: CONTOUR PLOT

Table 4: Evaluation parameters of formulation F1 to F17

Formulation Code	A: Pullulan	B: PEG	C: MDX	Thickness	Disintegration time	%CDR	Folding endurance	Surface pH
F1	200	4	150	0.26	49	98.46	>300	6.63
F2	300	3	100	0.18	30	98.93	>300	6.67
F3	400	4	100	0.25	58	98.24	>300	6.74
F4	300	2	150	0.16	35	98.78	>300	6.71
F5	400	2	100	0.25	52	98.85	>300	6.80
F6	200	2	100	0.12	12	99.49	>300	6.53
F7	300	3	100	0.17	30	98.95	>300	6.28
F8	200	3	50	0.09	9	99.58	>300	6.30
F9	400	3	50	0.22	42	98.65	>300	6.82
F10	200	3	150	0.15	25	99.04	>300	6.37
F11	300	3	100	0.16	30	98.91	>300	6.69
F12	300	2	50	0.14	18	99.32	>300	6.70
F13	200	4	100	0.10	20	98.9	>300	6.65
F14	300	3	100	0.16	31	98.94	>300	6.30
F15	400	3	150	0.28	54	98.52	>300	6.74
F16	300	4	50	0.13	29	98.74	>300	6.28
F17	300	3	100	0.18	29	98.92	>300	6.79

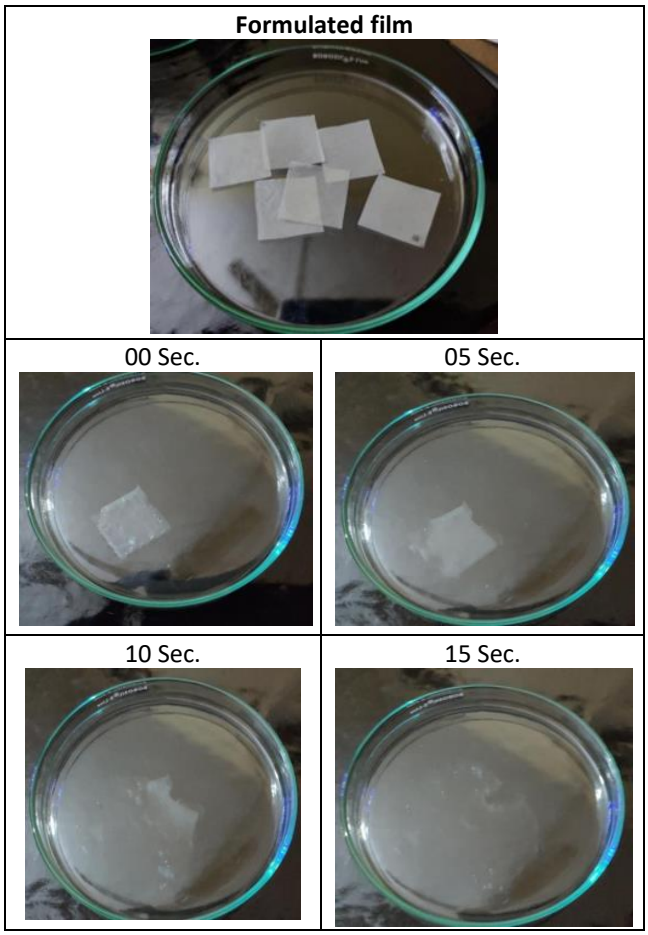

Figure 4: Disintegration of film

Films of F8 showed less thickness, less disintegration time and higher % cumulative drug release than films of other formulations. Hence Pullulan 200 mg and PEG 3ml were selected for optimized formulation. So, formulation was optimized using Box-Behnken design. Formulation F8 showed less thickness, lower disintegration time and desired physical evaluation parameter. So, the formulation F8 containing 200 mg Pullulan, 50 mg Maltodextrinand 3 ml PEG was considered to be optimized formulation. It was found that % CDR and disintegration decreases as the film forming polymer concentration increases and the thickness of film increases as the film forming polymer increases.

In-vitro drug release

USP type II apparatus was used for dissolution study in which 500 ml of 6.8 phosphate buffer used. The rpm and temperature are maintained at 50 rpm and 37± 0.5 °C respectively. While performing this evaluation sometimes film float over medium making difficult to perform and to avoid this sinker is used. Then the sample withdrawn at predetermined various time interval 0,2,4,6,8,10, and filter through Whatman filter paper and analyze using UV-Spectrophotometer at λmax at 225 nm. Sink condition were maintained throughout the experiment (Table 5).

Table 5: Dissolution data of formulation

Cumulative % drug release (containing 2 ml PEG formulation)							
Time (min)	0	2	4	6	8	10	12
F4	0	38.12	54.65	76.18	86.44	98.85	
F5	0	37.42	53.67	73.82	82.74	91.64	98.85
F6	0	40.12	60.2	80.15	99.49	-	-
F12	0	39.59	56.95	77.84	87.73	99.32	-
Cumulative % drug release (containing 3 ml PEG formulation)							
Time (min)	0	2	4	6	8	10	12
F2	0	37.73	54.95	80.85	93.43	96.06	98.95
F7	0	38.12	56.89	78.21	92.51	95.43	98.93
F8	0	42.15	62.23	82.26	99.58	-	-
F9	0	37.8	54.82	81.44	90.92	94.16	98.65
F10	0	38.42	55.35	68.08	82.57	99.04	-
F11	0	36.65	58.8	79.66	90.02	95.12	98.91
F14	0	37.59	57.11	79.56	89.73	95.84	98.94
F15	0	32.67	55.75	68.23	80.65	90.44	94.83
F17	0	38.33	55.5	78.4	88.9	96.8	98.92
Cumulative % drug release (containing 4 ml PEG formulation)							
F1	0	30.51	39.59	56.38	74.84	82.64	90.12
F3	0	27.95	36.12	53.23	68.86	86.67	94.42
F13	0	36.93	50.3	64.22	77.02	91.12	96.26
F16	0	34.82	48.42	61.87	75.86	90.54	95.43

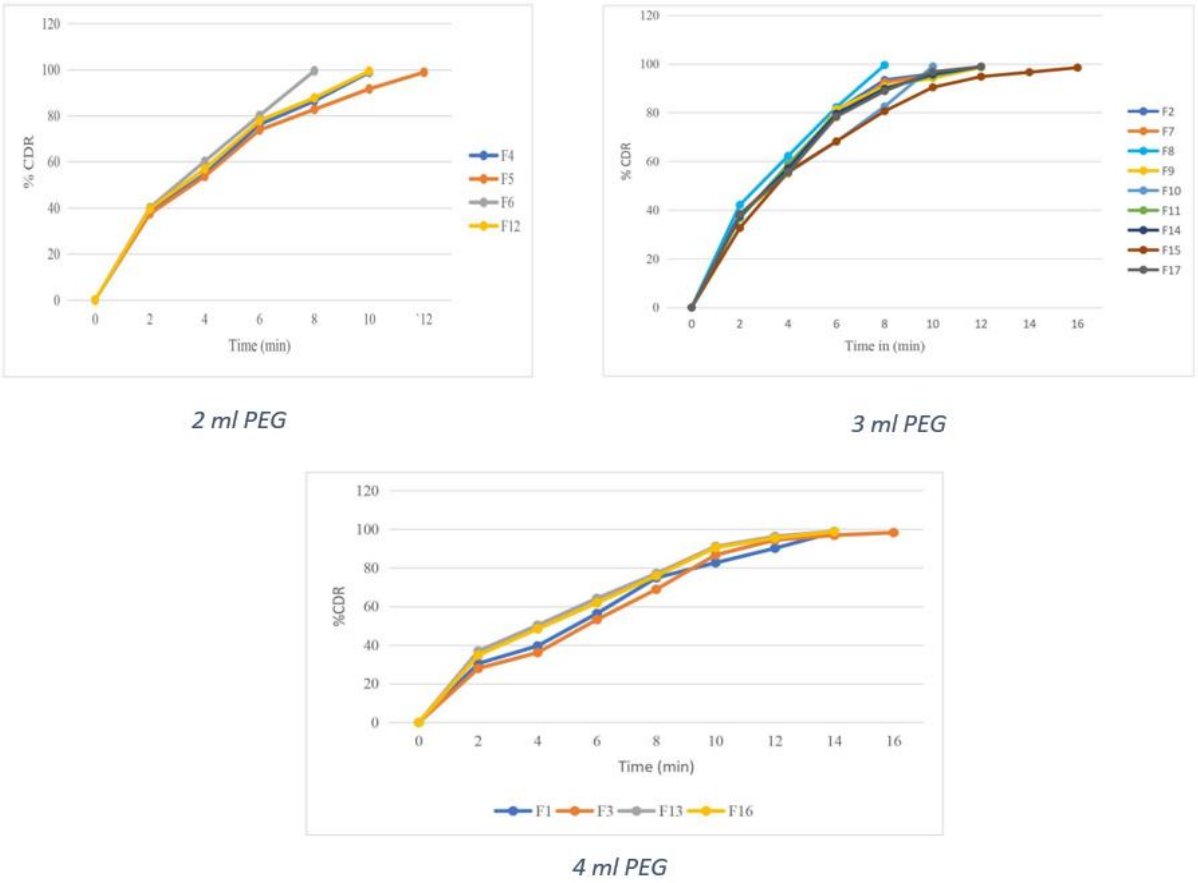

Figure 5: % CDR of formulation containing 2 ml PEG, 3 ml PEG, 4 ml PEG

SUMMARY AND CONCLUSION

The aim of study is to determine optimum combination of film forming polymer and concentration of polyethylene glycol for formulation of fast dissolving film. Different polymer was screened for film forming polymer capacity among them pullulan and maltodextrin were selected. Also, plasticizer was screened by evaluating disintegration time and folding endurance. Rizatriptan benzoate sample was found to be as per standard and identified by UV, FTIR and DSC. The polymers were identified by infrared spectroscopy. The compatibility study of drug and polymer was confirmed by FTIR and DSC. The fast dissolving was film prepared by solvent casting method and evaluated for thickness, folding endurance, pH, in-vitro disintegration time and in-vitro dissolution time. The formulation optimized by using Box-Behnken design. Formulation F8 containing pullulan 200 mg, maltodextrin 50 mg and polyethylene glycol 3 ml was considered to be optimized formulation. Formulation F8 shows lower disintegration time 9 seconds and higher % drug release of 99.58%. It was found that concentration of film forming polymer and polyethylene glycol increases which decrease the disintegration time and % drug release significantly. It can be concluded that Fast dissolving film of Rizatriptan Benzoate can be formulated by using Pullulan, Maltodextrin as film forming polymer and Polyethylene glycol as plasticizer. Hence, Rizatriptan benzoate can conveniently administered in the form of Fast dissolving film.

FUTURE SCOPE

- In-vivo study to determine bioavailability of Rizatriptan Benzoate
- IVIVC correlation of In-vitro drug release study and In-vitro bioavailability.
- Stability study as per ICH guideline
- In-vivo permeation study of formulated Fast dissolving film

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