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Formulation and Evaluation of Fast Dissolving Film of Rizatriptan Benzoate.

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Abstract: Rizatriptan benzoate is an anti migraine drug. The therapeutic activity of the drug can most likely be attributed to agonist effects at 5-HT1B/1D receptors. It is well absorbed from the gastrointestinal tract, but its oral bioavailability is low (45%) due to first-pass metabolism which makes it an ideal candidate for rapid release drug delivery system. Hence, an attempt was made to prepare and evaluate fast dissolving oral films containing Rizatriptan benzoate as a model drug by solvent casting method using hydrophilic polymers. Various formulations were developed with varying concentration of polymers like HPMC, PVA, PVP K30, Xanthan gum, Guar gum. Citric acid was used as a saliva stimulating agent and Propylene glycol as a plasticizer. The prepared oral films were evaluated for their physicochemical and mechanical parameters such as Physical appearance, surface pH, ,thickness uniformity, disintegration time, drug content uniformity, folding endurance, tensile strength, percentage elongation, *in-vitro* drug release. *In-vitro* release rate of Rizatriptan benzoate was studied in simulated saliva fluid (pH 6.8). From prepared formulations, the optimized plasticizer and polymer combination was selected and 3^2 factorial design was applied. On basis of factorial design, RSM and contour plots were applied. From factorial design batches the batch with lower disintegration time and good mechanical properties is optimized. This optimized batch was studied for its stability for 1 month. PG was optimized as plasticizer. It was observed that no single polymer was able to produce the film with desired quality hence polymer combination was used. The polymer combination of HPMC E 15 & PVA was optimized. On applying factorial design to this combination, batch with polymer ratio of 1:7 (HPMC: PVA) was optimized. The formulation was found stable after 1 month.

Keywords: Rizatriptan benzoate, Fast dissolving Films, HPMC, PVA

Introduction:[1-9]

Recent developments in the technology have presented viable dosage alternatives from oral route for pediatrics, geriatric, bedridden, nauseous or noncompliant patients, various bioadhesive mucosal dosage forms have been developed, which includes adhesive tablets, gels, ointments, patches and more recently the use of polymeric films for buccal delivery, also known as mouth dissolving films**.**[1]

By definition, a solid dosage form typically size of a postage stamp that dissolves or disintegrates quickly in the oral cavity resulting in solution or suspension without the need of water in a matter of seconds for the rapid release of one or more APIs is known as oral fast dissolving dosage form.[2,3] It consists of fast dissolving polymer film embedded with drug, which quickly hydrates and dissolves when placed on the tongue or in the oral cavity (i.e., buccal, palatal, gingival, lingual, or sublingual) to provide rapid local or systemic drug delivery without need of water. The mouth dissolving film is also known as fast dissolving film, quick dissolving film, rapid dissolving film or oral thin film.[4] In contrast to other existing, rapid dissolving dosage

forms, which consist of lyophilized product, the rapid films can be produced with a manufacturing process that is competitive with the manufacturing costs of conventional tablets**.**[5]

Why Rizatriptan Benzoate In Fast Dissolving Film?

Rizatriptan Benzoate is an anti migraine drug. It is more effective than other triptans as it achieved both Pain relief and Pain Freedom within 2 h after dosing than other oral triptans.[6]

It fits in the parameters for ideal characteristics for drug for FDF
The ideal characteristics for drug for FDF are: [2]
The drug to be incorporated should have low dose up to 40mg.
The dose of Rizatriptan Benzoate is 30mg/day.
The drugs with smaller or moderate molecular weight are preferable.
The molecular weight of Rizatriptan Benzoate is 391.5 gm/mol which is small molecule.
It should have good stability and solubility in water as well as in saliva.
Rizatriptan Benzoate is freely soluble in water and saliva.
It should be partially ionized at pH of oral cavity.
It should have ability to permeate oral mucosal tissue.

Fast dissolving films offer fast, accurate dosing in a safe, efficacious format that is convenient and portable, without the need for water or measuring devices.[7] Dissolution within oral cavity also permits intra-oral absorption, thus bypassing first pass effects.[8]

Migraine is a chronic neurological disorder characterized by recurrent moderate to severe headaches often in association with a number of autonomic nervous system symptoms. Approximately 15% of the population is affected by migraines at some point in 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, and sensitivity to light, sound, or smell. The pain is generally made worse by physical activity. Up to one-third of people with migraine headaches perceive an aura: a transient visual, sensory, language, or motor disturbance which signals that the headache will soon occur. Symptoms can be visual, sensory or motor in nature and many people experience more than one.[9]

Symptoms may include a wide variety of phenomena, including altered mood, irritability, depression or euphoria, fatigue, craving for certain food, stiff muscles (especially in the neck), constipation or diarrhea, and sensitivity to smells or noise. The pain is frequently accompanied by nausea, vomiting, sensitivity to light, sensitivity to sound, sensitivity to smells, 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 a sense of the world spinning, light-headedness, and confusion. Nausea occurs in almost 90% of people, and vomiting occurs in about one-third. Symptoms may include blurred vision, nasal stuffiness, diarrhea, frequent urination, pallor, or sweating. Swelling or tenderness of the scalp may occur as can neck stiffness. Often a feeling of pins-and-needles begins on one side in the hand and arm and spreads to the nose-mouth area on the same side. Numbness usually occurs after the tingling has passed with a loss of position sense.[9]

For this a dosage form which has Fast disintegration, Rapid release, faster absorption, quick on set of action is needed which is fulfilled by FDFs.

Hence formulation of fast dissolving films of rizatriptan benzoate is done.

Materials and Methods:

Rizatriptan benzoate was obtained as a gift sample form SMS Pharmaceuticals lmt, Hyderabad. HPMC E-15 were procured from Colorcorn Pvt Lmt, India, PVP K 30, PVA(cold soluble), Guar Gum and Xanthan Gum were procured from ACS Chemicals and all other ingredients were obtained from Astron Chemicals. All ingredients were of analytical reagent grade.

Experimental Work:

Solvent Casting Technique: [10, 11]

In this method, the water and the drug along with other excipients is dissolved in suitable solvent. Then both solutions are mixed and stirred and finally casted into the Petri plate and dried.

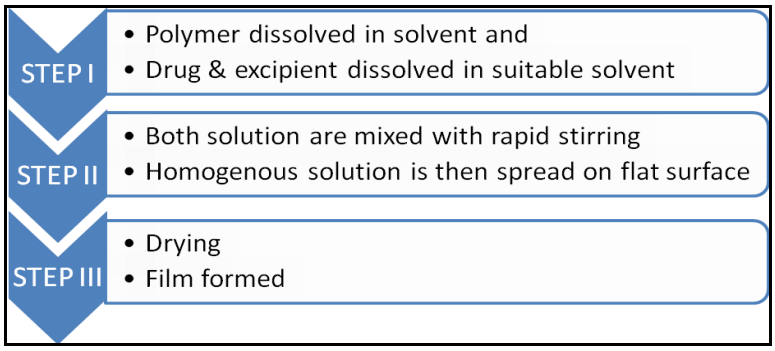


Fig I: Solvent Casting Method

Evaluation of the mouth dissolving film: [12-24]

Mouth dissolving film should be stiff, flat and should not curl on the edges. The mouth dissolving film strip must be robust enough to be removed from the unit-dose packaging and to be handled by the consumer without breaking. The film must also dissolve readily in order to deliver the active agent rapidly when placed in the oral cavity. Mechanical property of mouth dissolving film plays an important role in deciding all these things. Therefore, the mechanical property of mouth dissolving film is as important as its solubility rate. So the prepared mouth dissolving films were evaluated for the following parameters:

1. Film Separability:

The ease of film separation from the mould (separability) and disintegration time were considered for the selection of best film from various batches prepared (preliminary batches) as well as for the selection of the polymer for further studies.

Table I: Criteria for film separability:

Term	Code
Poor	-
Moderate	+
Good	++

2. Disintegration time: [12,13,14,15]

The film was kept in petri-dish filled with simulated saliva fluid pH 6.8 and time at which it starts to break or disintegrate is recorded as disintegration time.

3. Measurements of Mechanical Properties:

The mechanical properties of the film gives idea about to what extent the film can withstand the force or stress during processing, packaging, transport and handling. The measurement of mechanical properties gives an indication of the strength and elasticity of the film, reflected by the parameters, tensile strength, elastic modulus and elongation at break.

Table II: Mechanical Properties of Film:[16]

Type of polymer	Tensile Strength	Elastic Modulus	Elongation at break
Soft and Weak	Low	Low	Low
Hard and Brittle	Moderate	High	Low
Soft and Tough	Moderate	Low	High
Hard and Tough	High	High	High

A suitable film should have a relatively moderate tensile strength, high % elongation at break but a low elastic modulus. Mechanical properties of film were evaluated using Tensilometer, Ponco Machine Tools. Film strip with dimension 2x2 cm^2 and free from air bubbles or physical imperfections was held between two clamps positioned at certain distance. The force (gm) was applied by pulling one clamp. The values of mechanical properties were recorded when the film broke. Measurements were run in triplicate for each film. Three mechanical properties namely tensile strength, % elongation and elastic modulus of films were evaluated.

- **Tensile strength:**[12,17]

It is measured by Tensilometer. Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip.

T.S= load applied (gm)/ Cross-sectional area of film (cm^2)

- **% Elongation:**[12,17]

When stress is applied, a strip sample stretches and this is referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. Generally elongation of strip increases as the plasticizer content increases.

It is calculated as =Increase in length /Original length * 100

- **Young's Modulus:**[18]

Young's modulus, *E*, can be calculated by dividing the tensile stress by the extensional strain in the elastic (initial, linear) portion of the stress–strain curve:

$$E \equiv \frac{\text{tensile stress}}{\text{extensional strain}} = \frac{\sigma}{\varepsilon} = \frac{F/A_0}{\Delta L/L_0} = \frac{FL_0}{A_0 \Delta L}$$

Where

E is the Young's modulus (modulus of elasticity)

F is the force exerted on an object under tension;
A_0 is the original cross-sectional area through which the force is applied;
ΔL is the amount by which the length of the object changes;
L_0 is the original length of the object

4. Folding endurance: [12,17]

Folding endurance was determined by repeatedly folding the film at the same place till it break. The numbers of times the film can be folded at the same place without breaking give the value of folding endurance.

5. Thickness of film: [12]

The thickness of each sample was measured using a micrometer at five locations (center and four corners), and the mean thickness calculated.

6. Drug content uniformity: [19,20,21]

The film unit (n=3) of the dimensions 2 cm× 2 cm was placed in 100 ml of simulated saliva fluid pH 6.8.After complete solubilization, the solution was diluted appropriately, filtered and analyzed at 220nm using

UV-Visible Spectrophotometer (Shimadzu 1800). The average of three films was taken as the content of drug in one film unit.

7. In vitro dissolution studies:[22]

The simulated salivary fluid was taken as the dissolution medium to determine the drug release. The dissolution profile was carried out in a beaker containing 30 ml of the simulated salivary fluid (pH 6.8) as a dissolution medium, maintained at 37 ± 0.5°C. The medium was stirred at 100 rpm. Aliquots of the dissolution medium were withdrawn at determined time interval and the same amount was replaced with the fresh medium. Samples were assayed spectrophotometerically. The percentage of the drug dissolved at various time intervals was calculated and plotted against time.

8. Evaluation of Taste Masking:[23, 24]

In the present work, the taste acceptability was measured by a taste panel. Each formulation was given to a taste panel expert and was held in the mouth for 10-15 seconds, then spat out and the bitterness level was recorded. Volunteers were asked to gargle with distilled water between the film sample administrations. The scale mentioned in Table C was used further in the study for the taste evaluation of the film formulation.

Table III: Bitter Index Level

Numerical value	Scale
4	Strong bitter
3	Moderate to strong
2	Slight to moderate
1	Slightly bitter
0	Tasteless or taste masked

Calculation of dose of Rizatriptan Benzoate:

Oral dose of Rizatriptan is 5mg.
269.40mg Rizatriptan= 391.46mg of Rizatriptan benzoate
So,
5mg Rizatriptan= 5 x 391.46/269.40
= 7.265mg of Rizatriptan benzoate.
Each film should contain 7.265mg of Rizatriptan benzoate.
Area of each film= 2*2= 4cm^2
Area of petridish= πr^2
Where, r= radius of petridish =4.45cm
According to this, Area of petridish= 62.17cm^2
For a film, 4cm^2 contains 7.265mg Rizatriptan benzoate.
So, in a petridish of 62.17cm^2 contains,
= 62.17*7.265/4
= 112.91mg Rizatriptan benzoate.
≈113 mg Rizatriptan benzoate was taken

Formulations for Optimization of Plasticizer (PEG 400, PG, DBP, Glycerin):

Table IV: Batches for Plasticizer (PEG 400, PG, DBP, Glycerin) optimization

Ingredients (mg)	P1	P2	P3	P4
HPMC E15	200	200	200	200
Polyvinyl pyrrolidone K30 (PVP K30)	100	100	100	100
Polyethylene Glycol 400 (PEG 400)	116	-	-	-
Propylene Glycol (PG)	-	116		
Di-butyl phthalate (DBP)	-	-	116	-
Glycerin	-	-	-	116
Mannitol	36	36	36	36

Citric acid	36	36	36	36
Tween 80	q.s	q.s	q.s	q.s
Water	q.s	q.s	q.s	q.s

Evaluation Parameter For P1 To P4 Batches:

Table V: Evaluation Parameter For P1 To P4 Batches

Evaluation Parameter	**P1**	**P2**	**P3**	**P4**
1.Appearance	Poor	Good	Poor	Passable
2.Mechanical Properties:				
Folding endurance	40	200	150	150
Tensile strength(gm)	2	16.66	2.5	13.63
% Elongation	4.5	11.36	4.5	6.81
Tear resistance(gm/cm^2)	50	410	60	300
3. Thickness(mm)	0.13	0.12	0.1	0.11
4. Surface pH	7	7	7	7
5. Disintegration time (sec)	40	15	20	30

Discussion:

P1 batch contains PEG 400 as plasticizer. Films thus prepared were found to be sticky. They were not transparent but hazy. Tensile strength and folding endurance were less.

P2 batch contains PG as plasticizer. Films with good folding endurance and desired plasticity were obtained. They were transparent.

P3 batch contains DBP as plasticizer. Plasticity was found to be good but on addition of DBP to polymer solution, the solution became hazy and films produced were not transparent.

P4 batch contains glycerin as plasticizer. Films were found to be hard.

According to this, Batch P2 produced the films of desired quality hence PG is optimized as plasticizer.

Formulations for Optimization of Polymer (HPMC E 15, PVP K30, PVA, Guar Gum, Xanthan Gum):

Table VI: Batches for Polymer (HPMC E 15, PVP K30, PVA, Guar Gum, Xanthan Gum) optimization

Ingredients (mg)	**P5**	**P6**	**P7**	**P8**	**P9**
API (Rizatriptan benzoate)	112	112	112	112	112
HPMC E15	300	-	-	-	-
Polyvinyl pyrrolidone K30	-	300	-	-	-
Poly vinyl alcohol	-	-	300	-	-
Guar Gum	-	-	-	50	-
Xanthan Gum	-	-	-	-	50
Propylene Glycol	116	116	116	116	116
Mannitol	36	36	36	36	36
Citric acid	36	36	36	36	36
Tween 80	q.s	q.s	q.s	q.s	q.s
Water	q.s	q.s	q.s	q.s	q.s

Evaluation Parameter For P5 To P9 Batches:

Table VII: Evaluation Parameter for P5 to P9 Batches

Evaluation Parameter	**P5**	**P6**	**P7**	**P8**	**P9**
1.Appearance	Good	Sticky	Good	Sticky	Sticky
2.Mechanical Properties:					
Folding endurance	300	-	300	250	250
Tensile strength(gm)	25.22	-	30	2	0.09
% Elongation	13.63	-	18.18	2.27	4.54
Tear resistance(gm/cm^2)	400	-	610	40	30
3. Thickness(mm)	.09	-	0.1	0.1	0.11
4. Surface pH	7	-	7	7	7
5. Assay(%)	85.32	-	78.43	71.69	69.78
6. Disintegration time (sec)	5	-	25	30	45

In-vitro drug release:

Table VIII: In-vitro drug release for P5 to P9:

Time(min)	**%CDR**				
	P5	**P6**	**P7**	**P8**	**P9**
0	0	-	0	0	0
1	20.98	-	19.85	34.75	16.02
2	40.18	-	38.11	89.362	34.82
3	66.09	-	63.51	95.26	49.06
4	81.09	-	78.65	98.47	58.99
5	90.43	-	89.03	98.21	72.35

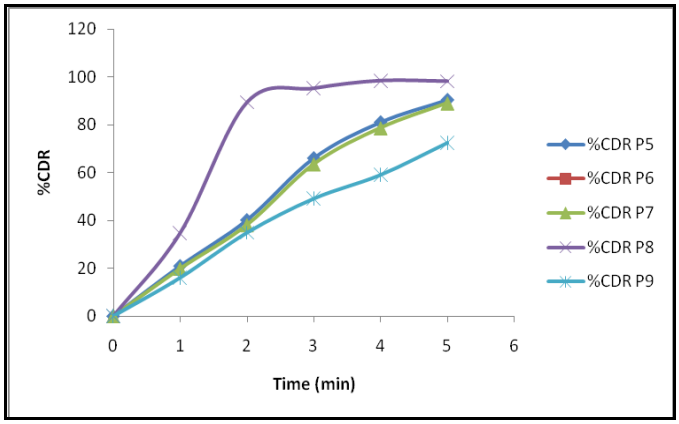


Fig II: %CDR for batches P5 to P9

Discussion:

P5 batch contains HPMC E15 which produced thin and plastic like film. It showed very fast disintegration time and drug release was found to be good.

P6 batch contains PVP K 30 which is highly hygroscopic and sticky material. Films prepared using PVP K30 showed poor separatibility from mould and complete peeling was not possible and it also had unacceptable physical characteristics. Visual appearances like transparency offered by these films were also very poor.

P7 batch contains PVA which produced soft film and drug release was found to be good. As

PVA is soft and tough polymer, Tensile strength was moderate and % elongation is high.

P8 batch contains Guar Gum which does not disperse uniformly in solvent (water). This results in development of clumps. The film separability is also affected. Uniform drug release is not obtained due to such clumps.

P9 batch contains Xanthan Gum. It dispersed uniformly. It produced white coloured films. On Contact with media the viscous solution is obtained which does not allow desirable drug release.

According to the results obtained of these batches, no individual polymer was able to produce the film of desired quality. To overcome this problem the combination of polymers were taken.

The combination of HPMC E15 with other polymers was chosen because HPMC E 15 has low viscosity and helps in faster disintegration of film.

Formulations for Optimization of Polymer Combination (HPMC E 15- PVP K 30, HPMC E 15-PVA, HPMC E 15-Guar Gum, HPMC E 15-Xanthan Gum)

Table IX: Batches for Polymer Combination (HPMC E 15- PVP K 30, HPMC E 15-PVA, HPMC E 15-Guar Gum, HPMC E 15-Xanthan Gum) optimization

Ingredients (mg)	**P10**	**P11**	**P12**	**P13**
API (Rizatriptan benzoate)	112	112	112	112
HPMC E15	200	210	267	267
Polyvinyl pyrolidone K30 (PVP K 30)	100	-	-	-
Poly vinyl alcohol (PVA)	-	90	-	-
Guar Gum	-	-	34	
Xanthan Gum	-	-	-	34
Propylene Glycol (PG)	116	116	116	116
Mannitol	36	36	36	36
Citric acid	36	36	36	36
Tween 80	q.s	q.s	q.s	q.s
Water	q.s	q.s	q.s	q.s

Evaluation Parameter for P10 To P13 Batches

Table X: Evaluation Parameter for P10 To P13 Batches

Evaluation Parameter	**P10**	**P11**	**P12**	**P13**
1.Appearance	Poor	Good	Poor	Average
2.Mechanical Properties				
Folding endurance	50	250	50	70
Tensile strength(gm)	0.83	20	1.81	2.72
% Elongation	2.27	9.09	4.54	4.54
Tear resistance(gm/cm^2)	20	410	40	60
3. Thickness(mm)	0.12	0.1	0.11	0.11
4. Surface pH	7	7	7	7
5. Assay(%)	72.85	84.23	79.20	69.49
6. Disintegration time(sec)	45	30	45	35

In vitro drug release for P10 to P13:

Table XI: In vitro drug release for P10 to P13:

Time(min)	%CDR			
	P10	**P11**	**P12**	**P13**
0	0	0	0	0
1	26.48	69.48	38.39	25.42
2	33.4	74.48	49.31	31.43
3	63.12	84.36	51.21	50.49
4	71.56	85.56	90.36	71.36
5	75.43	82.89		77.82

Discussion:

Batch P10 contains ratio of HPMC E 15 and PVP K30. Films produced were hard and smooth. There is no significant change in drug release profile as compared to individual polymer.

Batch P11 contains ratio of HPMC E 15 and PVA. Films produced were smooth and soft. Tensile strength was moderate whereas %elongation was found to be good. Moreover, the drug release profile was also good.

Batch P12 contains ratio of HPMC E 15 and Guar gum. Films produced were soft but surface was not uniform. The clumps of guar gum were observed. These clumps interfered in drug release profile of this batch.

Batch P13 contains ratio of HPMC E 15 and Xanthan Gum. Films produced were smooth. White spots were observed on surface of films. Drug release was slower than desired.

From above results it is concluded that the films produced by P11 batch possess desired characters. And hence the polymer ratio of HPMC E 15 and PVA is optimized.

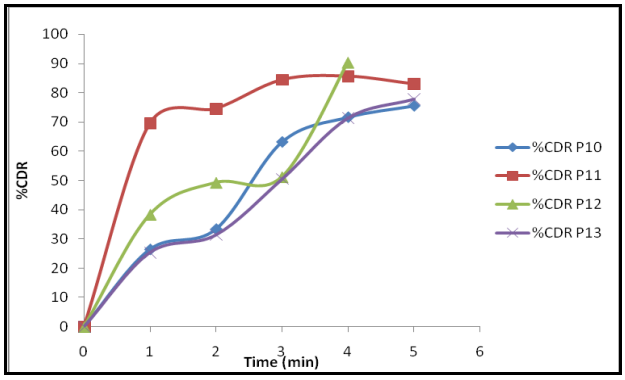


Fig III: %CDR for batches P10 to P13

Full factorial design 3^2 :

Table XII: Independent variables and Levels

Independent Variables	**Levels**		
X1(HPMC E 15)Coded value	-1	0	+1
Actual value	1	3	5
X2 (PVA) Coded value	-1	0	+1
Actual value	5	7	9

Factorial Design Formulation:

Table XIII: Values for ratio of X1 and X2 for F1 to F9:

Batch	Coded Value		Decoded Value	
	X1	X2	X1	X2
F1	-1	-1	1	5
F2	0	-1	3	5
F3	1	-1	5	5
F4	-1	0	1	7
F5	0	0	3	7
F6	1	0	5	7
F7	-1	1	1	9
F8	0	1	3	9
F9	1	1	5	9

Table XIV: Formula for F1 to F9 batches:

Ingredients (mg)	F1	F2	F3	F4	F5
API (Rizatriptan benzoate)	113	113	113	113	113
HPMC E15: PVA	1:5	3:5	5:5	1:7	3:7
Propylene Glycol (PG)	5	5	5	5	5
Mannitol	30	30	30	30	30
Citric acid	30	30	30	30	30
Tween 80	q.s	q.s	q.s	q.s	q.s
Water	q.s	q.s	q.s	q.s	q.s

Ingredients (mg)	F6	F7	F8	F9
API (Rizatriptan benzoate)	113	113	113	113
HPMC E15: PVA	5:7	1:9	3:9	5:9
Propylene Glycol (PG)	5	5	5	5
Mannitol	30	30	30	30
Citric acid	30	30	30	30
Tween 80	q.s	q.s	q.s	q.s
Water	q.s	q.s	q.s	q.s

Evaluation Parameters for F1 to F5:

Table XV: Evaluation Parameters for F1 to F5:

Parameter	F1	F2	F3	F4	F5
Appearance	Good	Good	Moderate	Good	Good
Separability	++	++	-	++	++
Folding Endurance	>200	>200	>150	>250	>250
Mechanical Properties					
Tensile Strength (kg/cm^2)	24.5	25.0	17.08	50.0	32.0
% Elongation	22.95	15.0	6.77	39.28	26.66
Tear Resistance (gm)	500	620	420	1200	670
Young's Modulus	111.36	116.66	254.97	128.20	120.30
Thickness (mm)	0.10	0.12	0.12	0.10	0.10
Surface pH	5.81	6.40	7.61	6.54	5.53
Disintegration Time (sec)	5	12	10	8	9
Assay (%)	107.3	87.24	75.7	93.59	90.62
Bitter Index	2	2	1	1	2

In Vitro drug release:

Table XVI: In Vitro drug release

Time (min)	%CDR				
	F1	**F2**	**F3**	**F4**	**F5**
0	0	0	0	0	0
1	35.28	40.32	39.89	40.21	38.2
2	41.3	45.15	55.27	59.79	47.78
3	66.05	69.59	68.15	75.56	69.75
4	74.83	75.02	74.82	84.32	72.16
5	86.19	88.24	85.17	93.21	86.29

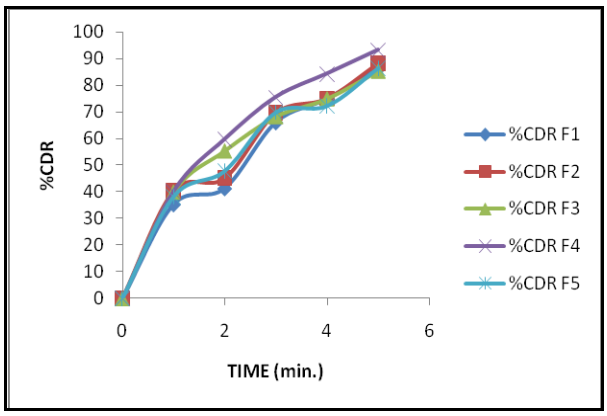


Fig IV: %CDR for batches F1 to F5

Evaluation Parameters for F6 to F9

Table XVII: Evaluation Parameters for F6 to F9:

Parameter	**F6**	**F7**	**F8**	**F9**
Appearance	Good	Good	Moderate	Good
Separability	+	++	+	+
Folding Endurance	>250	>250	>275	>200
Mechanical Properties				
Tensile Strength (kg/cm^2)	23.88	50.0	80.0	45.5
% Elongation	16.92	14.51	33.33	29.31
Tear Resistance (gm)	450	910	1140	850
Young's Modulus	141.18	344.58	242.42	155.47
Thickness (mm)	0.09	0.09	0.07	0.09
Surface pH	6.40	6.43	6.50	6.49
Disintegration Time (sec)	7	12	10	8
Assay (%)	112.86	91.27	88.78	89.47
Bitter Index	2	2	1	2

In Vitro drug release:

Table XVIII: In Vitro drug release for F6 to F9

Time (min)	%CDR			
	F6	**F7**	**F8**	**F9**
0	0	0	0	0
1	38.86	51.17	40.98	39.27

2	51.91	65.21	61.39	58.58
3	63.27	78.16	79.02	65.28
4	75.84	84.97	83.48	79.21
5	84.23	92.14	90.82	87.42

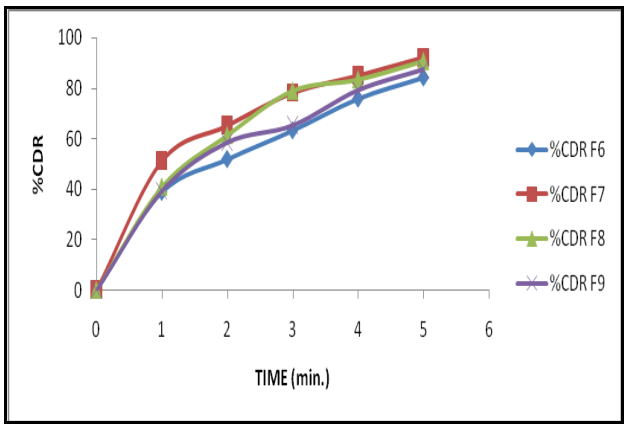


Fig V: %CDR for batches F6 to F9

Discussion:

Batch F1 and F2 produce films with good appearance but mechanical properties and drug release profile are not desirable. Batch F3 produce very rough films with low separability from petridish. Batch F5 possess good mechanical properties but drug release is lower than expected. Batch F6 does not have reproducibility. Batch F8 produced films with very high tensile strength which is not desirable. Batch F7 and F9 tend on curl slightly on separation from petri-dish which is not desired.

Batch F4 possess desirable mechanical properties i.e comparatively moderate tensile strength, low Young's Modulus and high %elongation. This produce soft but tough film

From the results, F4 Batch is considered as the optimized batch.

Regression Analysis for effect of X1 and X2 on Y1 and Y2:

Table XIX: Coefficient and p values for Disintegration Time:

Regression Statistics		
	Full Model	**Reduced Model**
Multiple R	0.9562	0.8223
R Square	0.9144	0.6762
Adjusted R Square	0.7719	0.5683
Standard Error	1.5122	2.0805
Observations	9	9

Anova				
		Regression	**Residual**	**Total**
df	F.M	5	3	8
	R.M	2	6	8
SS	F.M	73.36	6.8611	80.2222
	R.M	54.25	25.9722	80.2222
MS	F.M	14.6722	2.2870	
	R.M	27.125	4.3287	
F	F.M	6.4153		

	R.M	6.2663		
Significance F	F.M	0.0784		
	R.M	0.0339		
	Full Model		Reduced Model	
	Coefficients	P-value	Coefficients	P-value
Intercept	10.88	0.0023	10.44	5.4E-06
X1	2.0	0.0478	2.0	0.0500
X2	0.66	0.3592*	-	-
X11	1.66	0.2169*	-	-
X22	-2.33	0.1171*	-	-
X12	-2.75	0.0358	-2.75	0.038359

*Regression coefficients, statistically insignificant ($p > 0.05$)

Full Model Equation:

Disintegration Time (Y1) = $10.88 + 2.0X_1 + 0.66X_2 + 1.66\ X_{11} - 2.33X_{22} - 2.75X_{12}$
Reduced Model Equation:
Disintegration Time (Y1) = $10.88 + 2.0X_1 - 2.75X_{12}$

Discussion:

Here, there is positive sign for main effect of variable X1 which predicts Variable X1 (HPMC E 15) has most significant effect on the response (disintegration time). Whereas the interaction effect of X1X2 has negative sign which predicts that this interaction antagonises the response for disintegration time.

Table XX: Coefficient and p values for Young's Modulus:

Regression Statistics		
	Full Model	**Reduced Model**
Multiple R	0.9829	0.9646
R Square	0.9662	0.9305
Adjusted R Square	0.9100	0.8889
Standard Error	24.5646	27.3020
Observations	9	9

Anova				
		Regression	**Residual**	**Total**
df	F.M	5	3	8
	R.M	3	5	8
SS	F.M	51869.9	1810.26	53680.16
	R.M	49953.14	3727.018	53680.15
MS	F.M	10373.98	745.403	
	R.M	16651.05	745.403	
F	F.M	17.191		
	R.M	22.338		
Significance F	F.M	0.0203		
	R.M	0.0025		

	Full Model		**Reduced Model**	
	Coefficients	**P-value**	**Coefficients**	**P-value**
Intercept	110.22	0.0091	129.89	0.0004
X1	43.24	0.0229	43.24	0.0116
X2	-5.42	0.6264*	-	-
X11	74.35	0.0234	74.35	0.0119
X22	29.5	0.1880*	-	-
X12	-83.18	0.0065	-83.18	0.0017

*Regression coefficients, statistically insignificant ($p > 0.05$). Not considered in Reduced Model.

Full Model Equation:

Young's Modulus(Y2) = $110.22 + 43.24X_1 - 5.42X_2 + 74.35X_{11} + 29.5X_{22} - 83.18X_{12}$
Reduced Model Equation:
Young's Modulus (Y2) = $110.22 + 43.24X_1 + 74.35X_{11} - 83.18X_{12}$

Discussion:

Here, there is positive sign for the main effect of variable X1 which predicts Variable X1 (HPMC E 15) has most significant effect on the response (Young's Modulus). Whereas the interaction effect of X1X2 has negative sign which predicts that this interaction antagonises the response for Young's Modulus.

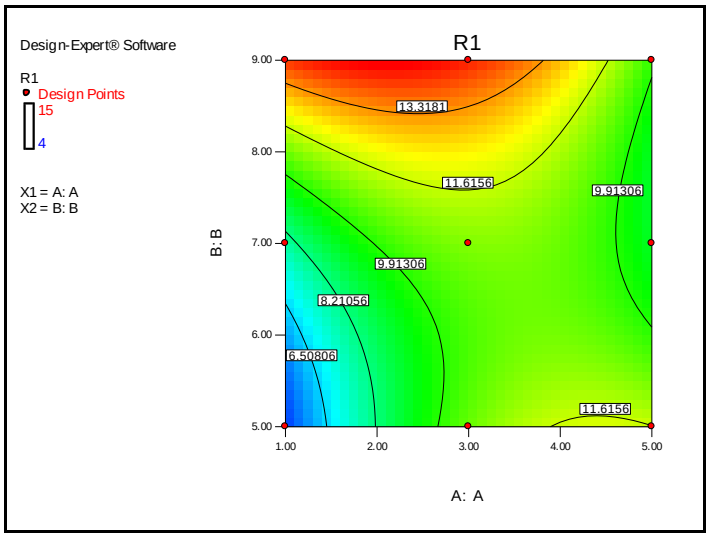
Contour Plot and Response Surface Plot for Each Response:

Response surface methodology (RSM) is a collection of mathematical and statistical techniques for empirical model building. By careful design of experiments, the objective is to optimize a response (output variable) which is influenced by several independent variables (input variables). An experiment is a series of tests, called runs, in which changes are made in the input variables in order to identify the reasons for changes in the output response. Experimental design has several advantages over the classical one-step approach. It improves performance characteristics, reduced cost, shortened development and testing times. This is achieved by isolating and better understanding those factors that mostly affect the outcomes. So researches can devote fewer resources for investigating less important factors.[25]

Contour Plot Surface plots were obtained for the measured response based on the model using Design-Expert® software. The relationship between the independent variables and the response can be further explained by using these surface plots.

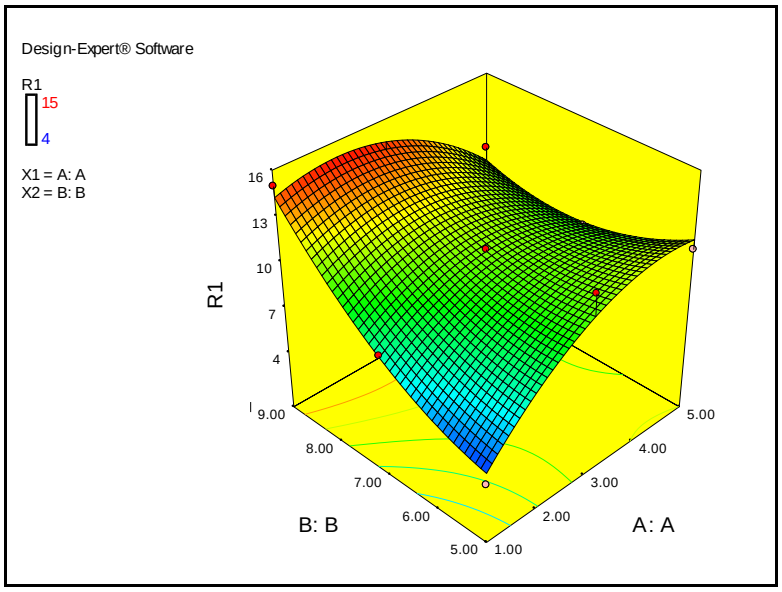
Generation of Contour plots, response surface plot and Overlay plot for responses:

Generation of Contour plots and response surface plot for response Disintegration Time



Here, R1 = Disintegration Time
A = Amount of HPMC E 15 in ratio of HPMC E 15 : PVA
B = Amount of PVA in ratio of HPMC E 15 : PVA

Fig VI: Contour Plot for Response R1 (Disintegration Time)



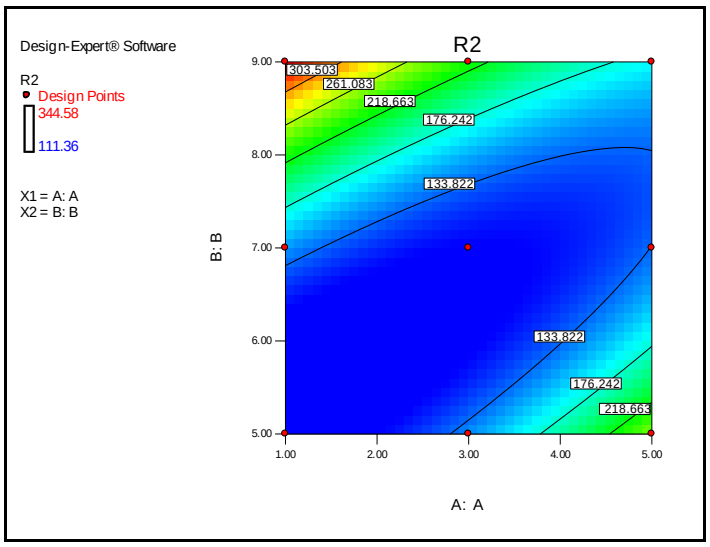
Here, R1 = Disintegration Time

A = Amount of HPMC E 15 in ratio of HPMC E 15 : PVA

B = Amount of PVA in ratio of HPMC E 15 : PVA

Fig VII: Response Surface Plot for Response R1 (Disintegration Time)

Generation of Contour plots and response surface plot for response Young's Modulus

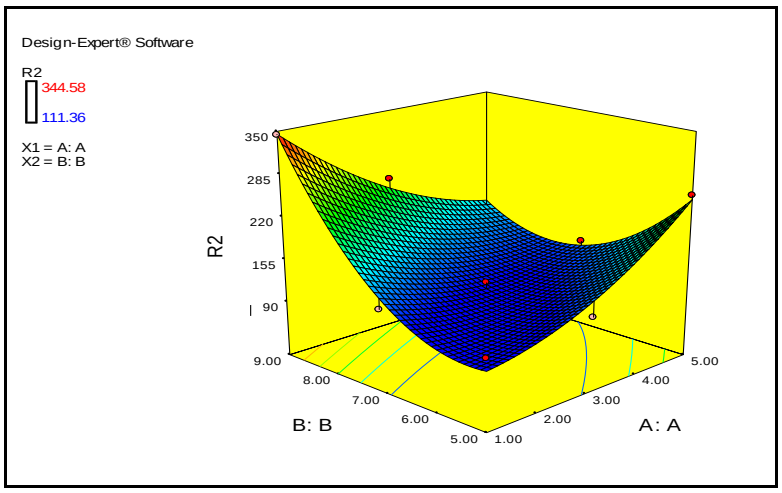


Here, R2 = Young's Modulus

A = Amount of HPMC E 15 in ratio of HPMC E 15 : PVA

B = Amount of PVA in ratio of HPMC E 15 : PVA

Fig VIII: Contour Plot for Response R2 (Young's Modulus)



Here, R2 = Young's Modulus

A = Amount of HPMC E 15 in ratio of HPMC E 15 : PVA

B = Amount of PVA in ratio of HPMC E 15 : PVA

Fig IX: Response Surface Plot for Response R2 (Young's Modulus)

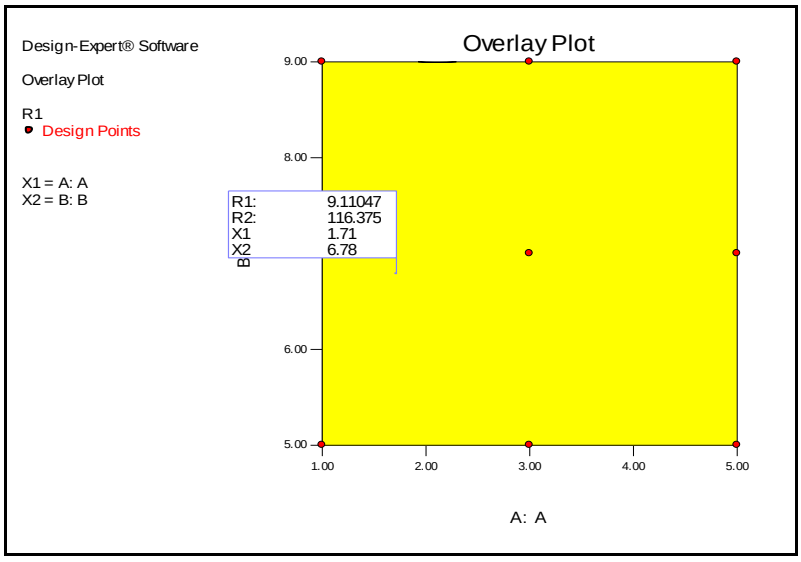
Discussion:

From Fig 6 and Fig. 8 it is observed that lower amount of HPMC E15 and higher amount of PVA gives optimum responses (R1, R2). As ratio of HPMC E 15: PVA is increased the responses (R1, R2) are also increased and vice versa.

Overlay Plot for check point batches:

Three check point batch was prepared to find the efficiency of full model equations generated previously using 3^2 full factorial designs.

1. Check point batch (C1) using HPMC E 15: PVA (X1 : X2) in ratio of 1.71 : 6.78



R1 = Disintegration Time

R2= Young's Modulus

A = Amount of HPMC E 15 in ratio of HPMC E 15 : PVA

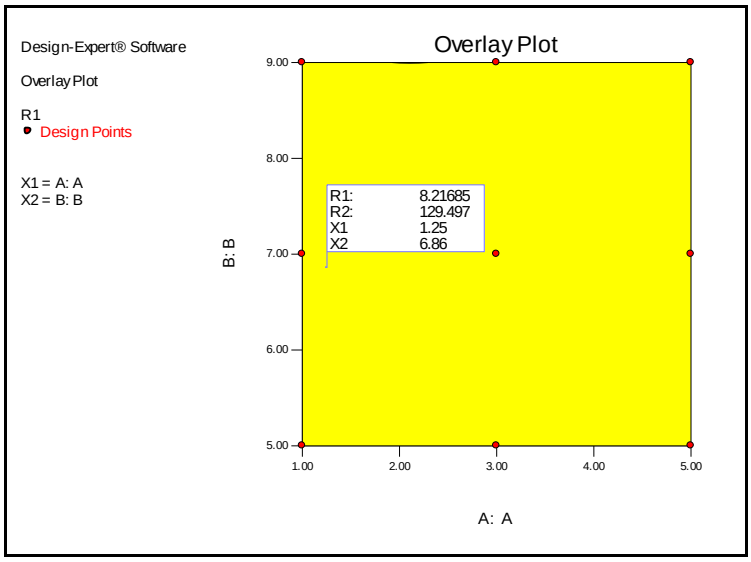
B = Amount of PVA in ratio of HPMC E 15 : PVA

Fig X: Overlay plot for C1

Table XXI: Comparison between the experimental and Practical values for the check point batch(C1)

Response	Check point batch	
	Predicted	**Experimental**
R1	9.11	8
R2	116.37	120.38

2. Check point batch (C2) using HPMC E 15: PVA (X1 : X2) in ratio of 1.25: 6.86



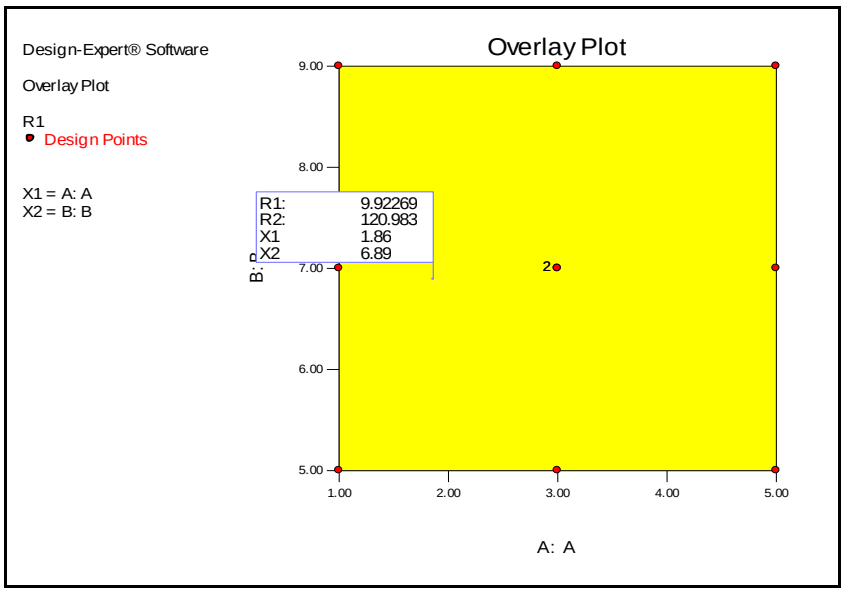
R1 = Disintegration Time
R2= Young's Modulus
A = Amount of HPMC E 15 in ratio of HPMC E 15 : PVA
B = Amount of PVA in ratio of HPMC E 15 : PVA

Fig XI: Overlay plot for C2

Table XXII: Comparison between the experimental and Practical values for the check point batch(C2)

Response	Check point batch	
	Predicted	**Experimental**
R1	8.21	9
R2	129.49	135.4

3 Check point batch (C3) using HPMC E 15: PVA (X1 : X2) in ratio of 1.86 : 6.89



R1 = Disintegration Time
R2= Young's Modulus
A = Amount of HPMC E 15 in ratio of HPMC E 15 : PVA
B = Amount of PVA in ratio of HPMC E 15 : PVA
Fig XII: Overlay plot for C3

Table XXIII :Comparison between the experimental and Practical values for the check point batch(C3)

Response	**Check point batch**	
	Predicted	**Experimental**
R1	9.92	11
R2	120.98	115.28

Stability Study:

Stability study of optimized batch F4 was carried out according to ICH guidelines. The condition of stability chamber was maintained at 40 ± 2 °C and 75 ± 5% RH. The stability studies were carried out for 1 month. A sample was collected after 1 month, it was observed for physical appearance, disintegration time, drug content and *in-vitro* drug release.

Table XXIV: Stability Study

Evaluation parameters	**F4 Batch**	
	Initial Data	**After 1 month**
Appearance	**Good**	**Moderate**
Separability	++	
Folding Endurance	>250	>200
Mechanical Properties		
Tensile Strength (kg/cm^2)	50.0	45.0
% Elongation	39.28	33.92
Tear Resistance (gm)	1200	1000
Young's Modulus	128.20	132.66
Thickness (mm)	0.10	0.10
Surface pH	6.54	6.43
Disintegration Time (sec)	8	7
Assay (%)	93.59	92.83
Bitter Index	1	1

Table XXV: In vitro Release after 1 month:

Time (min)	F4 Batch	
	Initial Data	After 1 month
0	0	0
1	40.21	41.28
2	59.79	55.48
3	75.56	69.32
4	84.32	81.75
5	93.21	89.13

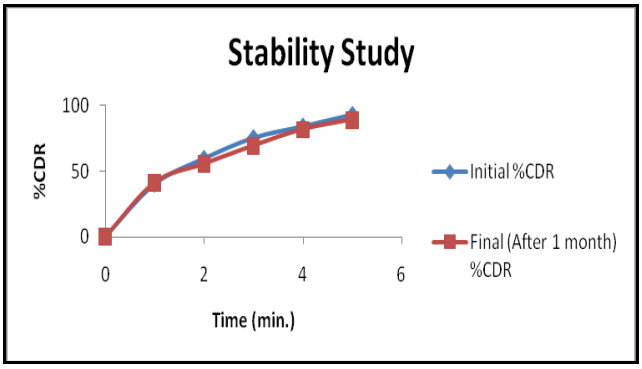


Fig XIII: In vitro Release after 1 month

Table XXVI: Comparison of stability study data

t-Test: Paired Two Sample for Means		
Observation	**Initial %CDR**	**After 1 month %CDR**
Mean	58.84833333	56.16
Variance	1184.042057	1058.1754
Observations	6	6
Pearson Correlation	0.998135567	
Hypothesized Mean Difference	0	
Df	5	
t Stat	2.371635721	
P(T<=t) one-tail	0.031911554	
t Critical one-tail	2.015048372	
P(T<=t) two-tail	0.063823108	
t Critical two-tail	2.570581835	

Discussion:

The t-test is applied for both initial and after 1 month %CDR of formulation F4 which is optimized. The result in table shows that there is no significance difference in %CDR of two formulations. The tabulated value is higher than the calculated value for both one and two tailed tests. This concludes that there is no significant difference between two formulations and the formulation after 1 month is stable.

Conclusion:

Rizatriptan Benzoate is an anti migraine drug which is formulated in fast dissolving dosage form. According to various formulations produced, P5 to P9 (single polymer batches) were not able to produce films with desired parameters. Hence batches P10 to P13 were formulated which had combination of polymers. From them, P11 batch was optimized which contained polymer combination of HPMC E 15: PVA. 3^2 factorial design was applied on basis of this batch and F1 to F9 batches were formulated. Various evaluation parameters were studied and F4 was concluded as optimized batch. Contour plots and response surface plots were plotted and studied which concluded that ratio of polymer chosen was optimum. F4 batch was kept for stability study and reading was taken after one month and t- test analysis was carried out. t-test result concluded that there was no significant change in readings after one month.

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