Int. J. Pharm. Investigation, 2020;10(4):479-485 *Original Article*

Formulation Development and Characterization of Rapid Mouth Dissolving Film of Frovatriptan Succinate

Pankaj Bhatt*, Suruchi Singh, Satish Kumar Sharma, Sani Rabiu
Department of Pharmacology, School of Pharmacy, Glocal University, Mirzapur Pole, Uttar Pradesh, INDIA.

ABSTRACT

Objectives: Aim of the present research work is to prepared rapid mouth dissolving film of frovatriptan Succinate. **Methods:** Rapid Dissolving Film is prepared by Solvent casting method, hydroxypropyl methylcellulose E3 and E15 are helpful in the film-forming polymer, plasticizer in propylene glycol disintegrant is croscarmellose sodium, the artificial sweetener in aspartame as, citric acid as saliva stimulant, xylitol as diluents and natural sweetener, wild cherry as a flavour and Brilliant blue dye for elegance was selected for Rapid Dissolving Film preparation. By prism, software result is obtained and then evaluated using analysis of variance (ANOVA). **Results:** The result suggested that the formulation containing 20% w/w aspartame, 10% w/w xylitol and 5% citric acid was found to effectively obscure the bitter taste of drug with best overall acceptability. The same composition of aspartame, citric acid and xylitol were used for further optimization using design of an experiment to continue obscuring the bitter taste of frovatriptan Succinate. Simple lattice mixture design which is helpful in drug formulation by using polymer plasticizer and disintegrant concentration for disintegration time-independent variable tensile strength and percentage elongation for the response. **Conclusion:** The effect of each variable, two and three-factor interactions were studied. The batches were numerically optimized to give a design space. Rapid mouth dissolving films are also found to behave better patient compliance in all the age groups.

Key words: Migraine, Rapid Dissolving Film, Solvent casting method, Stability studies, Frovatriptan Succinate.

Correspondence

Mr. Pankaj Bhatt
School of Pharmacy, Glocal University, Mirzapur Pole, Uttar Pradesh, INDIA.
Phone no: +91 9045781973
Email: pankajbhattb.pharma@gmail.com

DOI: 10.5530/ijpi.2020.4.84

INTRODUCTION

Migraine is more commonly found in women than in men. In percentage, it is 20.7% in female and 9% in male. It is an episodic neurovascular disorder that occurs by severe attacks; the symptoms of unilateral pulsatile headache are nausea, photophobia and phonophobia.[1] As it is related to prolonged disability and seen in Healthcare place. They are very painful and make a person weak.[2] It is the main issue responsible for absenteeism in the workplace or school.[3] Headache that occurs due to tension is maximum among people, followed by a migraine headache, but it is excruciating out of all these migraines are found most common.[4] The oral route is the most preferred route of administration for systemic effect. About 60% of all formulations are of the solid dosage form. Tablet is the most preferred dosage form due to ease of transportation, manufacturing and more patient compliance. After swallowing the conventional tablet, some patient faces some difficulties like a paediatric, geriatric and forbidden patient. To rectify this issue, a formulation was being developed, i.e. oral fast dissolving film.[5] Oral dissolving films can be used anytime in the absence of water. Fast dissolving film shows faster dissolution due to least integration time. Sweeteners and flavours are added in preparation fast dissolving films which help in curing the patients.[6,7]

Frovatriptan Succinate is a 5-HT receptor agonist which binds with high affinity to 5-HT_{1B} and 5-HT_{1D} receptors.[8] *In vitro*, frovatriptan Succinate shows a moderate affinity for the receptor 5-HT7, which is believed to contribute to its distinctive pharmacologic properties.[9] Frovatriptan succinate demonstrated higher binding affinity than sumatriptan at the human 5-HT_{1B} receptor (~4-fold) and a comparable affinity at the human 5-HT_{1D} receptor.[10] The absolute oral bioavailability of Frovatriptan succinate is 22%-30%. The mean time to reach peak plasma concentration (T_{max}) is approximately 2-3 hr. Food does not influence the pharmacokinetics of frovatriptan Succinate.[11]

MATERIALS AND METHODS

Materials

Frovatriptan Succinate has occurred for gift sample from Orchid Chemicals and Pharmaceuticals Limited, India. Hydroxypropyl Methylcellulose, Hydroxypropyl cellulose, Polyethylene glycol 400, Propylene glycol, Glycerol, Xylitol, Maltodextrin, Mannitol, Sodium Starch Glycolate, Crospovidone, Croscarmellose Sodium, Citric Acid, Aspartame were used of analytical grade.

Methods

The drug and excipients were individually weighed and dispensed. The polymer was slowly dissolved in water under constant stirring at 600 rpm, followed by the addition of plasticizer, sweetener, citric acid, disintegrant, drug, colour and flavour. The solution was stirred for 2 hr to ensure a perfectly homogeneous mixture is obtained. The foam formed after stirring was removed by sonicating and degassing the solution, to obtain the final solution for Rapid Mouth Dissolving Film (RDF) casting. The calculated amount of the solution was poured on Petri plates and specially fabricated rectangular glass plate. The Petri plates and rectangular glass plate was kept in an oven at 60°C for 4 hr for drying the solution. Rapid Mouth Dissolving Film (RDF) formed after drying were carefully removed and cut into the desired size. The Rapid Mouth Dissolving Film (RDF) were packed in Aluminium wraps and

sealed with the help of tagger sealer and stored until further evaluation was carried out.

Selection of Polymer, Diluent and Disintegrant

On drug-polymer compatibility, diluent and disintegrant studies Hydroxypropyl methylcellulose (HPMC), Hydroxypropyl cellulose (HPC), Polyvinylpyrrolidone (PVP) of different grades and ratios were used for the primary selection between the polymers diluent and disintegrant.

Evaluation of the rapid disintegrating films

Physical appearance/surface texture: After Visual inspection of the Rapid Mouth Dissolving Film (RDF) evaluation was done according to the surface texture or by feel or touch.

Thickness uniformity

By using digital Vernier calliper (Mitutoyo Japan) Thickness was measured.

Uniformity of dosage units

The films were tested for uniformity of dosage form by the UV-Spectrophotometric method. Three different Rapid Mouth Dissolving Film Rapid Mouth Dissolving Film (RDF) of the same formulation was dissolved in 100 ml of Phosphate buffer pH 6.8 medium; 2 ml of this solution was diluted up to 10 ml with Phosphate buffer pH 6.8 medium to give a 7.8 ppm solution. The absorbance of the solution was measured at 244 nm using a UV visible spectrophotometer (Perkin Elmer Lambda 20). The standard solution of the raw drug of the same concentration was used as a bracketing standard after every six samples. By finding a standard graph percentage of drug content was being calculated and the same steps are repeated to other Rapid Mouth Dissolving Film (RDF) and the average drug content and standard deviation of each formulation was determined. This procedure was repeated for all 14 DOE formulations.

Assay

Formulation of 20 films were taken to dissolve it in 100 ml volumetric flask with purified water as medium (Stock I). From the Stock I solution equivalent to a single dose was calculated and was diluted with 100 ml of purified water. 2 ml of the solution is diluted till 10ml with distilled water and its absorbance was measured at 244 nm using a UV visible spectrophotometer (Perkin Elmer Lambda 20). The standard solution of the raw drug of the same concentration was used as a bracketing standard after every ten samples. The % drug content in each formulation was calculated using a standard graph. This procedure was repeated for every formulation and the assay was calculated.

In vitro disintegration

Each film that contains 10 ml of Phosphate buffer with pH 6.8 is placed in a petri dish. The time taken by each film when it starts to disintegrate was recorded. Average and standard deviations from 3 Rapid Mouth Dissolving Film (RDF) were measured and recorded.

In vivo disintegration

Rapid dissolving film is carried out in healthy volunteers (ageing 25-40 years, n=6) *in vivo* disintegration time. Before performing the test, the volunteers were aware of the steps and aim of the test. They were told that before placing the piece of Rapid Mouth Dissolving Film (RDF) on their tongue, they need to rinse their mouth. They were asked to monitor for the time required by the film to disintegrate and wash off thoroughly. *In vivo* disintegration times of the selected optimized batches were only carried out due to safety reasons.

In vitro dissolution

A suitable house method was used for *in vitro* drug release studies of Rapid Mouth Dissolving Film (RDF), for dissolution to be carried out in USP type-I (basket apparatus) of pH 6.8 medium with 500 ml of Phosphate buffer. The medium was maintained with a temperature of 37±0.5°C stirred at 100 rpm. The samples were withdrawn at an interval of 2, 5, 10, 15, 20 min and 30 min time. At each time interval, 10 ml of the sample was collected and is replaced with the same amount of medium. The samples were analysed in UV/Visible spectrophotometer (Perklin Elmer Lambda 20), bracketing standard after every six samples were measured which was prepared by dissolving the same amount of drug in 500 ml Phosphate buffer pH 6.8 medium.

Solid-state form of drug by X-Ray Diffractometer (XRD)

The form of input drug and the drug in the formulation was studied with the help of an X-ray diffractometer. The drug in the formulation must not recrystallize; if the drug in the formulation recrystallizes it gives a non-elegant appeal to the film.

Surface morphology of the formulation by Scanning Electron Microscopy (SEM)

The surface morphology of the optimized formulation was studied with the help of Scanning Electron Microscopy (LEO 400).

Stability studies

Stability studies of the formulation were carried out under accelerated stability conditions (40±2, 75±5% R.H.) and normal condition (25±2°C, 75±5% R.H.) for four weeks. The stability samples were withdrawn at two weeks and four weeks duration and were tested for physical appearance, assay and *in vitro* disintegration time are shown in Table 5. The samples were loaded in LDPE (open condition) and sealed aluminium packs (closed condition).

RESULTS

Selection of Polymer, Diluent and Disintegrant

Polymer, Diluent and Disintegrant Selection are shown in Table 1. PEG 400, Citric acid, Aspartame shows 60% that's for the best polymer. HPMC E3:E15 (85:15) shows 50% that's for the best diluent and best disintegrant.

Result of Polymer, Plasticizer, Diluent Selection Trials

Polymer has tested for different properties like Film-forming property, Appearance, Peelability, *in vitro* disintegration time and results are in Table 2. Plasticizers has tested for different properties like Folding endurance, Tensile strength (N), Percentage elongation, *in vitro* Disintegration time (sec) and results are in Table 2. Diluent has tested for different properties like Recrystallization, Texture, *in vitro* disintegration time (sec) and results are in Table 2.

Disintegration time, Tensile Strength, Percent elongation response as a response

The analysis of variance (ANOVA) result for Disintegration time, Tensile Strength, Percent elongation response presented in Table 3.

In vitro disintegration

The *in vitro* disintegration time of film was increases as the amount of Citric acid and Aspartame increases and increase in concentration of plasticizer decreased disintegration time but after excessive amount of

Table 1: Initial trials for polymer, diluents and disintegrant selection.

Excipients	Ingredients	RDF-I				
		1/01	**1/02**	**1/03**	**1/04**	**1/05**
	1. Drug	7.82%	7.82%	7.82%	7.82%	7.82%
	2. HPC EF	7.82%	-	-	-	-
	3. HPC LF	-	60%	-	-	-
	4. HPMC E3LV	-	-	60%	-	-
	5. HPMC E15LV	-	-	-	60%	-
Polymer	6. PVP	-	-	-	-	60%
	7. PEG 400	10%	10%	10%	10%	10%
	8. Citric acid	10%	10%	10%	10%	10%
	9. Aspartame	10%	10%	10%	10%	10%
	10. Brilliant Blue	0.03%	0.03%	0.03%	0.03%	0.03%
	11. Wild Cherry	2.15%	2.15%	2.15%	2.15%	2.15%
		3/01	**3/02**	**3/03**		
	1. Drug	7.82	7.82	7.82		
	2. HPMC E3: E15 (85:15)	50%	50%	50%		
	3. Propylene glycol	10%	-	-		
	4. Maltodextrin	10%	-	-		
Diluent	5. Mannitol	-	10%	-		
	6. Xylitol	-	-	10%		
	7. Citric acid	10%	10%	10%		
	8. Aspartame	10%	10%	10%		
	9. Colour	0.03%	0.03%	0.03%		
	10. Flavor	2.15%	2.15%	2.15%		
		3/01	**3/01**	**3/01**	**3/01**	**3/01**
	1. Drug	7.82%	7.8%	7.82%	7.8%	7.82%
	2. HPMC E3, E15 (85:15)	45%	45%	45%	45%	45%
	3. Propylene glycol	10%	-	-	-	-
	4. Xylitol	10%	-	-	-	-
	5. Sodium starch glycolate	5%	-	-	-	-
	6. Croscarmellose sodium	-	5%	-	-	-
Disintegrant	7. Crospovidone XL	-	-	5%	-	-
	8. Crospovidone XL 10	-	-	-	5%	-
	9. Kollidone CLSF	-	-	-	-	5%
	10. Citric acid	10%	10%	10%	10%	10%
	11. Aspartame	10%	10%	10%	10%	10%
	12. Brilliant Blue	0.03%	0.03%	0.03%	0.03%	0.03%
	13. Wild Cherry	2.15%	2.15%	2.15%	2.15%	2.15%

The polymers selected for the initial trial are HPC EF, HPC LF, HPMC E3LV, HPMC E15LV, PVP, PEG 400, Citric acid, Aspartame, Brilliant Blue, Wild Cherry.

The diluents selected for the initial trial are HPMC E3: E15 (85:15), Propylene glycol, Maltodextrin, Mannitol, Xylitol, Citric acid, Aspartame, Colour, Flavour.

The suitable disintegrates for the initial trial are HPMC E3, E15 (85:15), Propylene glycol, Xylitol, Sodium starch glycolate, Croscarmellose sodium Crospovidone XL, Crospovidone XL 10, Kollidone CLSF, Citric acid, Aspartame, Brilliant Blue, Wild Cherry.

polymer increase, the film became brittle so there was slight decrease in disintegration time. Results of different batches are shown in Table 4.

In vivo disintegration

The *in vitro* disintegration time of different batches was found to be between 31-124 sec. Results of different batches are shown in Table 4.

In vitro dissolution

In vitro drug release study of batches was performed in USP Dissolution Apparatus-I at 37 ± 0.5°C and 100 rpm using 500 ml of PBS pH 6.8 buffer for 30 min. Cumulative % drug release of different batches at the end of 5 min was found to be between 85.9 to 97.6%. Results of different batches are shown in Table 5.

Solid-state form of drug by X-Ray Diffractometer (XRD)

The X-Ray Diffractometer (XRD) results (Figure 1) also confirm the interactions and formation of a single homogenous phase by the appearance of the amorphous halo characteristic of single co-amorphous dispersions. X-ray diffractograms (XRD) of Optimized Formulation and

Table 2: Result of Polymer, Plasticizer, Diluent Selection Trials.

Excipients	Properly tested	RDF-I		
		1/06	1/07	1/08
	1. Film-forming property	1	1	1
Polymer	2. Appearance	1	1	1
	3. Peelability	1	1	2
	4. *In vitro* disintegration time	182	171	163
		1/08	1/09	1/10
	1. Folding endurance	127	231	153
	2. Tensile strength (N)	5.95	11.57	8.81
Plasticizer	3. Percentage elongation	2.3%	8.7%	3.7%
	4. *In vitro* Disintegration time (sec)	161	165	176
		3/02	3/02	3/03
	1. Recrystallization	No	Yes	No
	2. Texture	Rough	-	Smooth
Diluent	3. *In vitro* disintegration time (sec)	156	-	137

The *in vitro* disintegration time and texture of RDF-I-3/03 was found to be acceptable.

The different formulations like RDF-II-1/6, RDF-II-1/7, RDF-II-1/8 were selected for panel testing and found to be overall accepted.

Table 4: Result of *in-vitro/ in-vivo* Disintegration DOE Batches.

Evaluation parameter	Method/time	Formulation	D.T. (sec)
Disintegration	1. *In-vitro*	RDF-III-1/1	31.5±0.5
		RDF-III-1/2	48±1
		RDF-III-1/3	51±1
		RDF-III-1/4	67.5±2
		RDF-III-1/5	35.5±1.5
		RDF-III-1/6	31.5±0.5
		RDF-III-1/7	42±1
		RDF-III-1/8	66.5±1.5
		RDF-III-1/9	52.5±0.5
		RDF-III-1/10	68.5±0.5
		RDF-III-1/11	124.5±1.5
		RDF-III-1/12	48.5±1.5
		RDF-III-1/13	112.5±0.5
		RDF-III-1/14	58.5±0.5
	2. *In-vivo*	RDF-II-1/6	17.16
		RDF-II-1/7	18.66
		RDF-II-1/8	16.33

In-vitro/ in-vivo disintegration time of different batches RDF III and RDF II

Table 3: ANOVA for Mixture Special Cubic Model for Disintegration Time Response, Tensile Strength Response and Percentage Elongation Response.

Time Response	Source	ANOVA Result				Comment
		Sum of Squares	Mean Square	*F* Value	*p*-value Prob > F	
Disintegration Time Response (ANOVA for Mixture Special Cubic Model	1. Model	9847.943	1641.324	69.39755	<0.0001	Significant
	2. Linear Mixture	6542.62	3271.31	138.3157	<0.0001	
	3. AB	870.5254	870.5254	36.80707	0.0005	
	4. AC	490.6039	490.6039	20.74344	0.0026	
	5. BC	682.3541	682.3541	28.85092	0.0010	
	6. ABC	147.9374	147.9374	6.255006	0.0409	
	7. Residual	165.5572	23.65103			
	8. Lack of Fit	79.05724	26.35241	1.218609	0.4114	not significant
	9. Pure Error	86.5	21.625			
	10. Core Total	10013.5				
Tensile Strength Response	1. Model	35.1224	5.853733	37.18432	< 0.0001	Significant
	2. Linear Mixture	33.25962	16.62981	105.6366	< 0.0001	
	3. AB	1.259292	1.259292	7.999326	0.0255	
	4. AC	0.118113	0.118113	0.750284	0.4151	
	5. BC	0.797967	0.797967	5.06888	0.0591	
	6. ABC	0.675196	0.675196	4.289005	0.0771	
	7. Residual	1.101973	0.157425			
	8. Lack of Fit	0.813673	0.271224	3.763086	0.1165	not significant
	9. Pure Error	0.2883	0.072075			
	10. Cor Total	36.22437				
Percentage Elongation Response	1. Model	15.81714	3.163428	36.00903	< 0.0001	Significant
	2. Linear Mixture	12.98774	6.493868	73.91914	< 0.0001	
	3. AB	2.218838	2.218838	25.25684	0.0010	
	4. AC	0.028382	0.028382	0.323075	0.5854	
	5. BC	0.543001	0.543001	6.180928	0.0377	
	6. Residual	0.702808	0.087851			
	7. Lack of Fit	0.573358	0.143339	4.429183	0.0893	not significant
	8. Pure Error	0.12945	0.032363			
	9. Cor Total	16.51995				

Different model values were presented as mean ± S.D. (n=3).

Table 5: Result of *in-vitro* Dissolution of DOE Batches.

	Time	RDF-III-1/1	RDF-III-1/2	RDF-III-1/3	RDF-III-1/4	RDF-III-1/5	RDF-III-1/6	RDF-III-1/7	RDF-III-1/8	RDF-III-1/8	RDF-III-1/9	RDF-III-1/10	RDF-III-1/11	RDF-III-1/12	RDF-III-1/13	RDF-III-1/14
In vitro Dissolution	2 min	74.9%	83.7%	79.4%	85.3%	85.5%	79.1%	77.8%	84.2%	96.2%	84.2%	83.3%	87.5%	91.2%	78.1%	85.6%
	5 min	89.3%	93.5%	95.2%	95.8%	93.1%	87.6%	85.9%	96.2%	99.8%	96.2%	92.6%	93.8%	97.6%	93.5%	92.6%
	10 min	98.2%	99.8%	100.7%	99.1%	98.7%	94.4%	95.2%	99.8%	100.4%	99.8%	98.1%	99.4%	98.6%	99.7%	99.4%
	15 min	98.7%	100.3%	101.2%	99.7%	99.3%	98.7%	99.6%	100.4%	100.4%	100.6%	99.4%	100.7%	99.6%	100.2%	101.7%
	20 min	99.1%	102.1%	101.3%	99.7%	100.6%	100.3%	99.6%	100.4%	100.1%	101.4%	99.6%	101.4%	99.8%	100.4%	102.5%
	30 min	99.1%	102.3%	101.3%	99.3%	100.6%	100.4%	99.7%	100.1%		101.7%	99.5%	101.7%	99.9%	100.4%	102.8%

In vitro Dissolution profile of different DOE Batches RDF 1 to RDF 14

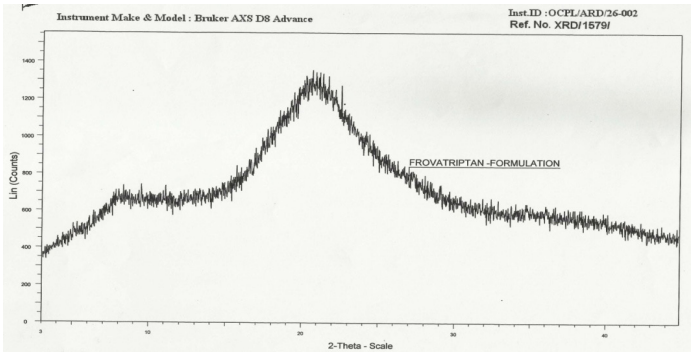

Figure 1: X-Ray Diffractometer (XRD) Result of Optimized Formulation.

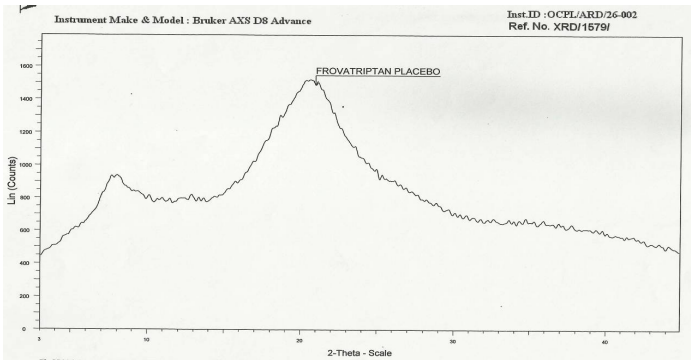

Figure 2: X-Ray Diffractometer (XRD) Result of Optimized Batch Placebo Formulation.

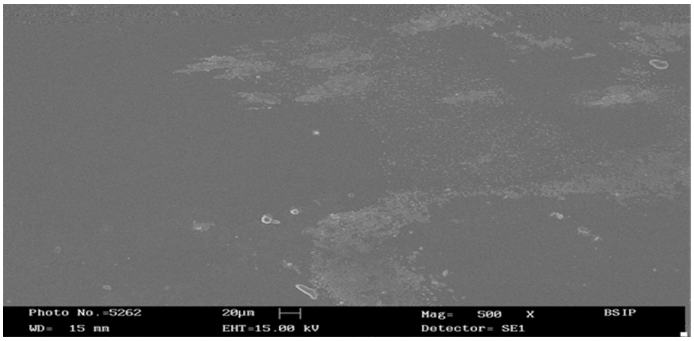

Figure 3: Scanning Electron Microscope (SEM) Image of Rapid Mouth Dissolving Film (RDF) at 500x magnification

Optimized Batch Placebo Formulation Frovatriptan Succinate Rapid Mouth Dissolving Film (RDF) are given in Figure 1 and 2.

Scanning Electron Microscopy (SEM)

SEM images of Frovatriptan Succinate Rapid Mouth Dissolving Film (RDF) are presented in Figure 3. SEM of Frovatriptan Succinate Rapid Mouth Dissolving Film (RDF) exposes discrete, elongated flake-like structures with rough edges covered on their surfaces by fine particles. Some structures are large with parallelogram shape. It also reveals the hard and thick nature of the drug particles. In contrast, Frovatriptan Succinate complex observed by SEM is soft and thin.

Stability studies

Accelerated Stability Studies optimized after 4 weeks and it showed good stable condition. Results of Stability studies of different batches are shown in Table 6.

Table 6: Result of Accelerated Stability Studies.

Storage condition	Duration	Type	Colour change	Assay	*In-vitro* disintegration time (sec)
40±2°C, 75±5% R.H.	Two weeks	Open	Yes	95.41±0.67	35±0.34
40±2°C, 75±5% R.H.	Two weeks	Closed	No	98.87±2.64	31±0.5
40±2°C, 75±5% R.H.	Four weeks	Open	Yes	94.79±0.94	37±0.73
40±2°C, 75±5% R.H.	Four weeks	Closed	No	97.62±1.93	33±1.5

Stability data of different formulations were presented as mean ± S.D. (n=3).

DISCUSSION

The physico-chemical characteristics of the drug were investigated and had a similarity with the internal specifications. The working λ_{max} was determined by using a UV spectrophotometer and was found to be 244nm, which complied with the internal specifications (λ_{max} 245nm).[12]

The taste masking of the films was done by optimizing the concentration of aspartame (sweetener), citric acid (saliva stimulant and flavour) and xylitol (natural sweetener and diluents). The tastes of the optimized films were panel tested by a group of 6 healthy volunteers. The selected formulations after the panel testing were evaluated statistically to see if there was any significant difference in the three formulations.[13] The evaluation was done applying one way ANOVA using the Kruskal-Wallis test. Post-test, the formulations were compared to each other using Dunnett's multiple comparison tests. Prism 5.0 software was used for calculation and analysing the results. The concentration of aspartame, citric acid and xylitol from the most desirable batch was selected and kept constant in further formulation optimization, to mask the taste of the drug effectively.

For the optimization procedure, a three-level Simplex lattice Mixture design was used. Three factors, concentration of Polymer (HPMC) (A), Plasticizer (Propylene Glycol) (B) and Disintegrant (C), were used in the design and the responses were *in vitro* disintegration time (Y1), Tensile strength (Y2) and Percentage elongation (Y3).[14]

Based on a Simplex lattice mixture design, a total of 14 batches were prepared by solvent casting method and evaluated based on *in vitro* disintegration time, Tensile strength and Percentage elongation. The *in vitro* disintegration time of different batches was found to be between 31-124 sec. The tensile strength of various batches was found to be in the range of 5.35 to 10.20 MPa. The Percentage elongations of various batches were found to be in the range of 2.58 to 5.97%. *In vitro* drug release study of batches was performed in USP Dissolution Apparatus-I at 37 ± 0.5°C and 100 rpm using 500 ml of PBS pH 6.8 buffer for 30 min. Cumulative % drug release of different batches at the end of 5 min was found to be between 85.9 to 97.6%.[15]

The Optimized batch (O.B.) Rapid Mouth Dissolving Film (RDF)-III-1/7 was determined by using the software Design Expert (Version 8.0.4.1). The optimized batch (O.B.) was prepared with concentrations of Polymer, Plasticizer and disintegrant at 43.33, 8.33 and 3.33 respectively by solvent casting method. Optimized batch (O.B.) showed *in vitro* disintegration time of 42 sec, Tensile strength of 7.36 MPa and Percentage elongation of 4.66%.

The results of Scanning Electron Microscope (SEM) (Figure 3) showed that uniformity in size and shape of frovatriptan succinate rapid mouth dissolving film. The Scanning Electron Microscope (SEM) of Rapid Mouth Dissolving Film (RDF) at 500X demonstrated the characteristic amorphous aggregates and presence of the defined shape of crystals. The Rapid Mouth Dissolving Film (RDF) prepared from solvent casting method showed an almost clear, transparent glassy and homogenous film with wholly dissolved into the polymer matrix.[16]

The X-Ray Diffractometer (XRD) spectrum of Optimized Batch Placebo Formulation of fravotriptan Succinate showed (Figure 2). The X-Ray Diffractometer (XRD) results (Figure 1) also confirm the interactions and formation of a single homogenous phase by the appearance of the amorphous halo characteristic of single co-amorphous dispersions.[16] The incorporation of RBD-ascorbic acid co-amorphous dispersions in fast dissolving oral film was intended to provide a simple, easily administered dosage form for the application inside the mouth. The formulated film was found to have an acceptable transparent appearance and mechanical properties, disintegration and dissolution.[17] Almost complete dissolution from the film was attained within 10 min. Also, the drug was found to be stable in the film for up to 12 weeks at 40°C and 75% RH which could be attributed to compatibility between polymers used in the film (PEG 400 and HPMC). This increased phase stability possibly occurred through extending the supersaturation state.

The optimized rapid mouth dissolving film (RDF) formula obtained by the model was chosen for testing the physico-chemical stability. Stability study of the optimized batch was carried out at accelerated condition and was found to be stable with no colour change when packed and sealed in aluminium foil, for four weeks.[17]

CONCLUSION

From the present study, it may be concluded that the Rapid dissolving films of Frovatriptan Succinate can be prepared by the solvent casting method using HPMC E3 and E15 in 85:15 ratio respectively by using propylene glycol as plasticizer, croscarmellose sodium as a disintegrant and xylitol as a natural sweetener and diluents. The final formula was optimized by simplex lattice mixture design using Stat-Ease design expert software to give the optimized batch. The optimized batch (O.B.) prepared with concentrations of Polymer, Plasticizer and disintegrate at 43.33, 8.33 and 3.33 respectively by solvent casting method. Optimized batch (O.B.) showed *in vitro* disintegration time of 42 sec, Tensile strength of 7.36 MPa and Percentage elongation of 4.66%.

ACKNOWLEDGEMENT

Special thanks to, higher authorities of Glocal University, Saharanpur to help and provide moral support for this research work.

CONFLICT OF INTEREST

The authors declare no Conflict of interest.

ABBREVIATIONS

FTIR: Fourier Transform Infrared Spectroscopy; **RDF:** Rapid dissolving film; **DOE:** Design of experiment; **SEM:** Scanning Electron Microscope; **HPMC:** Hydroxypropyl methylcellulose; **HPC:** Hydroxypropyl cellulose; **PVP:** Polyvinylpyrrolidone.

REFERENCES

1. Silberstein SD, Stiles MA, Young WB. Atlas of Migraine and Other Headaches. 2nd ed. London: Taylor and Francis Group. 2005.

2. Burch R, Rizzoli P, Loder E. The prevalence and impact of migraine and severe headache in the United States: Figures and trends from government health studies. Headache. 2018;58(4):496-505.
3. Macgregor AE. Menstrual migraine: A clinical review. J Fam Plann Reprod Health Care. 2007;33(1):36-47.
4. Saylor D, Steiner TJ. The global burden of headache. Scanning Electron Microscope in Neurol. 2018;38(2):182-90.
5. Siddiqui M, Garg G, Sharma P. A Short Review on A Novel Approach in Oral Fast Dissolving Drug Delivery System and Their Patents. Adv Biol Res. 2010;5(6):291-303.
6. Chaudhari VA, Sarode SM, Sathe BS, Vadnere GP. Mucoadhesive buccal drug delivery system: A review. Int J Pharm Sci. 2014;5(2):142-59.
7. Shimoda H, Taniguchi K. Preparation of fast dissolving oral thin film containing dexamethasone: A possible application to antiemesis during cancer chemotherapy. Eur J Pharm Biopharm. 2009;73(3):361-5.
8. Comer MB. Pharmacology of the selective 5-$HT_{1B/1D}$ agonist frovatriptan. Headache. 2002;42(2):47-53.
9. Brown AM, Ho M, Thomas DR, *et al.* Functional effects of frovatriptan (VML 251), sumatriptan and naratriptan on human recombinant 5-HT_1 and 5-HT_7 receptors. Headache. 1998;38:376.
10. Buchan P. The pharmacokinetics of frovatriptan (VML 251/SB 209509), a potent selective 5-HT1B/1D agonist, following single dose administration by oral and intravenous routes to healthy male and female volunteers. Func Neurol. 1998;13:177.
11. Buchan P, Keywood C, Wade A, *et al.* Clinical pharmacokinetics of frovatriptan. Headache. 2002;42(2):54-62.
12. Abualhasan M, Mansour J, Jaradat N, Zaid A, Khadra I. Formulation and Development of a Validated UV-Spectrophotometric Analytical Method of Rutin Tablet. Int Sch Res Notices. 2017;1-7. doi: 10.1155/2017/2624947
13. Chattopadhyay S, Raychaudhuri U, Chakraborty R. Artificial sweeteners: A review. J Food Sci Technol. 2014;51(4):611-21.
14. Chaudhary H, *et al.* Development and optimization of fast dissolving oro-dispersible films of granisetron HCl using Box-Behnken statistical design. Bull Fac Pharm Cairo Univ. 2013;51(2):193-201.
15. Gohel M, *et al.* Application of Simplex Lattice Design and Desirability Function for the Formulation Development of Mouth Dissolving Film of Salbutamol Sulphate. Curr Drug Deliv. 2009;6(5):486-94.
16. Löbmann K, *et al.* Amino Acids as Co-Amorphous Stabilizers for Poorly Water Soluble Drugs-Part 1: Preparation, Stability and Dissolution Enhancement. Eur J Pharm Biopharm. 2013;85(3):873-81.
17. Kawakami K. Modification of Physicochemical Characteristics of Active Pharmaceutical Ingredients and Application of Supersaturatable Dosage Forms for Improving Bioavailability of Poorly Absorbed Drugs. Adv Drug Deliv Rev. 2012;64(6):480-95.

Article History: Submission Date : 29-08-2020; Revised Date : 25-10-2020; Acceptance Date : 21-11-2020.
Cite this article: Bhatt P, Singh S, Sharma SK. Formulation Development and Characterization of Rapid Mouth Dissolving Film of Frovatriptan Succinatew. Int. J. Pharm. Investigation, 2020;10(4):479-85.