AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Formulation Development Evaluation and Optimization of Orodispersible Tablets of Frovatriptan for The Treatment of Migraine

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ABSTRACT

The aim of present research work is to formulate and evaluate Oral dispersible tablets of frovatriptan using various diluents and superdisintegrants and to optimize the formulation. Frovatriptan is a triptan drug used for the treatment of migraine headaches. The drug excipient compatibility study was done and no interactions were found, DSC & XRD studies were carried out. The tablets were formulated by direct compression method using Spray dried lactose, Manito, Microcrystalline cellulose (MCC), Starch as diluents and Crospovidone, Cross-Carmel lose sodium, Sodium starch glycol ate as superdisintegrants. The pre-compression parameters like bulk density, tapped density, Carr's Index, Haunters ratio and angle of repose were determined and all the formulations were found to be within IP limits. The post compression parameters like the hardness, thickness, friability, weight variation, and disintegrating time, wetting time, water absorption ratio and drug content for all the formulations were carried out and results were found to be as per USP limits. *In-vitro* drug release and kinetics studies were carried out for all the formulations, of those the formulation F_{33} containing Cross providing (5%) and mannitol as diluent, has shown better release and follows first order kinetics. The formulations were optimized by 2^2 factorial design and the ANOVA study was carried out and normal plot, half normal plot and overlay plot were plotted. The tablets were stored at 40±2˚C/75 ± 5% RH for three months to assess the stability of optimized formulation.

Keywords: Frovatriptan, Crospovidone, Crosscarmellosesodium, Sodium starch glycolate, MCC, Spray dried lactose, starch, Magnesium stearate, Talc, Aerosil and aspartame.

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Received 31 December 2017, Accepted 09 January 2018

Please cite this article as: Yella S *et al.*, Formulation Development Evaluation and Optimization of Orodispersible Tablets of Frovatriptan for The Treatment of Migraine. American Journal of PharmTech Research 2018.

INTRODUCTION

Oro-dispersible tablets/fast dissolving/ mouth dissolving tablets are one among them, which show rapid activity by dispersing in mouth itself and doesn't have water requirement. They are different form the drugs that are absorbed from other parts of gastro-intestinal tract. But here the solubilisation occurs in the saliva itself which on further passage into gastro-intestine shows dissolution of drug.

They are termed differently based on their functionality as rapid dissolving/fast dissolving/fast dis-integrating/Mouth dissolving tablets. The term oro-disperssible tablets were coined by European pharmacopeia. Thus the tablets get dispersed in the mouth itself with-in three munities before swallowing. These are standard dosage forms to United Statespharmacopeia. And the standard pertaining to these drugs is described in it. The primary ingredient they comprise is super dis-integrant which allows the tablet to disintegrate rapidly with-in one minute and makes it possible to swallow.

Migraine is neurological disease which is characterized by mild to severe headache that lasts from 1 hour to several hours with other autonomic nervous system symptoms. It is a Greek word meaning pain on one side of the head. It is caused in pulsating nature on one side of the head lasting from 2 to 72 hours. Hence Trptans are employed as orodispersible tablets to rapidly treat the headaches by dispersing in mouth. [1]

MATERIALS AND METHOD

Frovatriptan was obtained as a gift sample from Azakem labs ltd, Hyderabad, Crosscarmellose sodium, Sodium starch glycolate (SSG), Cross povidone, Microcrystalline cellulose, Mannitol, Spray dried lactose, Starch were obtained from Signet chemical corp. Mumbai, Aspartame, Aerosil, Talc, Magnesium stearate were obtained from S.D fine chemicals, Mumbai and Potassium dihydrogen ortho phopshate, Sodium hydroxide were obtained from Narmada chemicals.

Methods:

Calibration curve for Frovatriptan in 6.8 phosphate buffer:

100mg of Frovatriptan was accurately weighed into 100 ml volumetric flask and dissolved in small quantity of methanol. The volume was made up to 100 ml with pH 6.8 phosphate buffer to get a concentration of (1000µg/ml) SS-I. From this, 1 ml was withdrawn and diluted to 100ml with 6.8 phosphate buffer to get a concentration of (10 µg/ml) SS-II. From the standard stock solution (SS-II), 2ml, 4ml, 6ml, 8ml were withdrawn and volume was made upto 10ml with 6.8 phosphate buffer to give a concentration of 2, 4, 6 & 8µg/ml. Absorbance of these solutions was measured

against a blank of 6.8 phosphate buffer at 227nm.

Drug – excipient compatibility studies by IR:

Infra Red spectroscopy is one of the most powerful analytical techniques to identify functional groups of a drug. The pure drug and its formulation were subjected to IR studies. In the present study, the potassium bromide disc (KBr pellet) method was employed. DSC & XRD studies were also conducted on Frovatriptan pure drug samples.

Formulation of oro-dispersible tablets of Frovatriptan:

All the ingredients were weighed accordingly and passed through # 60 mesh sieve separately. The drug and diluents were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside. Then the other ingredients were mixed in geometrical order and passed through coarse sieve(#44mesh) and the tablets were compressed using hydraulic press. Compression force of the machine was adjusted to obtain the hardness in the range of 3-4 kg/cm^2 for all batches. The formulations are shown in Table1 & Table 2

Table 1: Formulation Of Orodispersitablble Tablets Of Frovatriptan Containing Various Diluents

Form code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
Frovatriptan	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
SSG	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Starch	100	120	140	160	-	-	-	-	-	-	-	-	-	-	-	-
Mannitol	-	-	-	-	100	120	140	160	-	-	-	-	-	-	-	-
MCC	-	-	-	-	-	-	-	-	100	120	140	160	-	-	-	-
Spray dried lactose(SDL)	-	-	-	-	-	-	-	-	-	-	-	-	100	120	140	160
Aspartame	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Aerosil	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Mg stearate	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4

Table 2: Formulations of Frovatriptan Using Various Superdisintegrants:

Form code	F17	F18	F19	F20	F21	F22	F23	F24	F25	F26	F27	F28	F29	F30	F31	F32	F33
Frovatriptan	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
SSG	4	6	8	10	12	14	16										
CCS								1	2	4	6	8	10				
CP														4	6	8	10
SDL	160	160	160	160	160	160	160	160	160	160	160	160	160	160	160	160	160
Aspartame	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Aerosil	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Mg stearate	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4

EVALUATION STUDIES

Recompression Parameters:

Method Preparation of Mixed Blend of Drug and Excipients

All the materials were passed through sieve no. 80. Required quantity of each ingredient was taken for each specified formats given in the formulation and all the ingredients were subjected to grinding to a required degree of fineness (except magnesium stearate and talc). The powdered blend was evaluated for flow properties as follows. The values are shown in Table 4.

Table 4: Data of Pre-Compression Parameters Evaluation Of Frovatriptan

Formulation	Derived properties		Flow properties		
	Bulk density	Tapped Density	Angle of Repose	Carr's index	Hausner's Ratio
F1	0.365	0.432	28.11	15.509	1.18
F2	0.357	0.429	26.2	16.783	1.2
F3	0.373	0.44	27.41	15.227	1.17
F4	0.35	0.401	25.82	12.718	1.14
F5	0.366	0.441	28.32	17.006	1.2
F6	0.374	0.438	26.42	14.611	1.17
F7	0.384	0.456	27.12	15.789	1.18
F8	0.326	0.386	29.09	15.544	1.18
F9	0.313	0.379	26.11	17.414	1.21
F10	0.386	0.461	28.41	16.268	1.19
F11	0.339	0.402	27.2	15.671	1.18
F12	0.323	0.396	26.18	18.434	1.22
F13	0.356	0.428	28.12	16.822	1.2
F14	0.328	0.412	29.02	20.388	1.25
F15	0.361	0.442	27.11	18.325	1.22
F16	0.368	0.432	26.32	14.814	1.17
F17	0.341	0.421	28.11	19.002	1.23
F18	0.339	0.406	27.12	16.502	1.19
F19	0.31	0.392	26.19	20.918	1.26
F20	0.345	0.394	28.2	12.436	1.14
F21	0.359	0.44	26.14	18.409	1.22
F22	0.363	0.452	28.04	19.911	1.24
F23	0.372	0.432	27.14	13.888	1.16
F24	0.382	0.461	26.25	17.136	1.2
F25	0.318	0.392	28.11	18.877	1.23
F26	0.32	0.402	27.32	20.398	1.25
F27	0.358	0.44	27.12	18.636	1.22
F28	0.314	0.395	26.18	20.506	1.25
F29	0.383	0.463	28.04	17.278	1.2
F30	0.342	0.432	27.14	20.833	1.26
F31	0.385	0.462	26.32	16.664	1.2
F32	0.367	0.453	28.18	18.984	1.23
F33	0.374	0.446	27.38	16.143	1.19

Angle of repose

Angle of repose is determined by using funnel method. The accurately weighed blend is taken in a funnel. The height of the funnel is adjusted in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug-excipient blend is allowed to flow through the funnel freely on to the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation. Angle of Repose less than 30 ° shows the free flowing of the material. The values are given in Table 4.

$$\theta = \tan^{-1} (h / r)$$

Bulk density:

Apparent bulk density is determined by pouring a weighed quantity of blend into graduated cylinder and measuring the volume and weight. The values are shown in Table 4

The bulk density was calculated by using the below mentioned formula

$$D_b = M/V_0$$

Where, **M** is the mass of powder, **V0** is the bulk volume of the powder

Tapped density:[6]

It is determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder is allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 second intervals. The tapping is continued until no further change in volume is noted. The results are shown in Table 4.

The tapped density was calculated using the following formula,

$$D_T = M/VT$$

Where, **M** is the mass of powder, V_T is the tapped volume of the powder

Compressibility index:[6]

The simplest way for measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index(I) which is calculated as follows,

Carr's Index (I) = Db/Dt

The value between 13-19% indicates a powder with usually good flow characteristics, whereas above 21% indicate poor flow ability. The values are shown in Table 4.

Hausner's Ratio[6]

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula

Hausner's Ratio = Dt/Db

Where $\mathbf{D_t}$ is tapped density and $\mathbf{D_b}$ is bulk density

Lower Hausner's ratio (<1.25) indicates better flow properties and higher Hausner's ratio (>1.25) indicates poor flow properties. The values are given in Table 4.

Weight variation test:[7]

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. First the total weight of 20 tablets from each formulation is determined and the average is calculated. The individual weight of the each tablet is also determined to find out the weight variation. The values are given in Table 5.

Table 5: Data Of Post Compression Parameters Of Frovatriptan Tablets

Formulation	Avg Weight (mg)	Thickness (mm)	Hardness Kg/cm^2	Friability (%)	Disintegration time(se)	Drug content	Wetting time	Water absorption ratio
F1	135.32	3.12	2.28	0.29	42	96.32	30	0.181
F2	151.95	3.98	2.52	0.61	36	97.42	28	0.194
F3	174.22	3.48	2.86	0.54	38	96.78	27	0.2
F4	192.94	3.26	3.26	0.68	40	95.93	29	0.25
F5	133.4	4.28	2.86	0.18	32	97.44	24	0.26
F6	153.45	4.02	2.92	0.37	36	95.337	30	0.192
F7	172.62	3.85	3.26	0.54	38	96.72	23	0.213
F8	194.26	4.64	2.67	0.36	39	98.46	26	0.242
F9	135.12	4.22	2.58	0.69	37	98.6	25	0.244
F10	154.63	3.82	3.18	0.81	35	.96.99	23	0.26
F11	172.84	3.76	2.62	0.24	39	95.14	26	0.22
F12	192.92	3.88	3.18	0.67	34	95.55	25	0.24
F13	132.68	4.3	3.24	0.18	35	97.74	28	0.194
F14	153.86	4.08	2.76	0.81	39	96.89	29	0.185
F15	172.66	3.98	3.08	0.25	32	92.86	24	0.23
F16	199.18	4.12	3.28	0.59	37	97.45	23	0.24
F17	199.62	3.94	3.18	0.64	30	96.33	20	0.272
F18	202.69	4.28	3.72	0.42	36	94.73	30	0.193
F19	204.08	3.64	3.21	0.38	35	95.33	28	0.201
F20	207.52	3.98	3.18	0.52	39	98.46	27	0.211
F21	209.11	4.12	3.42	0.26	37	95.77	25	0.22
F22	210.05	3.86	3.58	0.14	32	97.78	23	0.231
F23	213.62	4.14	3.86	0.24	30	97.32	18	0.29
F24	198.86	3.52	3.28	0.05	36	94.65	28	0.176
F25	199.29	3.96	3.51	0.19	38	95.55	29	0.202
F26	196.99	3.74	3.68	0.54	32	94.82	30	0.181

F27	199.84	3.28	3.28	0.31	39	95.02	28	0.194
F28	200.52	3.98	3.18	0.25	34	95.89	27	0.2
F29	201.06	4.36	3.52	0.02	38	96.02	29	0.25
F30	199.92	3.78	3.68	0.21	30	92.82	24	0.26
F31	200.05	3.48	3.12	0.35	29	95.21	30	0.192
F32	199.59	4.28	3.29	0.38	27	97.85	23	0.213
F33	200.10	3.96	3.52	0.26	26	99.24	26	0.242

Tablet hardness:[7]

The hardness of tablet is an indication of its strength. It is the force required to break a tablet by compression in the radial direction. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation is determined by Monsanto hardness tester, Pfizer hardness tester etc. The values re given in Table 5.

Tablet friability:[7]

Roche friabilator is employed for finding the friability of the tablets. Weigh the 20 tablets from each batch and place in Roche friabilator that will rotate at 25 rpm for 4 minutes. All the tablets are dedusted and weighed again. The percentage of friability can be calculated using the formula. The values of friability are shown in Table 5.

% Friability = [(W1-W2)100]/W1

Where, W1= initial weight, W2 = final weight

Thickness and Diameter:[3]

Tablet thickness and diameter can be measured using a simple procedure. Five tablets are taken and their thickness is measured using Vernier callipers. The thickness and diameter is measured by placing tablet between two arms of the Vernier calipers. The thickness values are given in Table 5.

In-Vitro Disintegration time:[3]

The test for disintegration was carried out in Electrolab USP disintegration test apparatus. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 liter beaker containing pH 6.8 buffer solution at 37°C ± 1°C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted. The values are given in Table 5.

.**Drug content uniformity:**[4]

The tablets were tested for their drug content uniformity. At random 10 tablets were weighed and powdered. The powder equivalent to 5 mg was weighed accurately and dissolved in 100ml of

suitable buffer solution. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatmann No.41 filter paper. Then the dilute the solution to obtain 10µg solution. The absorbance of the diluted solutions was measured at 224nm. The values are given in Table 5.

Wetting time:[1]

The tablet was placed on a filter paper which was immersed in the buffer solution containing a colored dye and the time taken for the tablet to get completely wet was measured by sorption of the colored dye. The values are shown in Table 5.

Water absorption ratio:[1]

The tablet was weighed initially and the weight was noted as (w1) then it is placed in petri plate containing distilled water or buffer solution and the water absorption capacity of the tablet was determined by weighing the tablet at regular intervals and that weight is taken as final weight (w2). The water absorption ratio can be calculated by the formula. The values are given in Table 5.

$$\text{Ratio} = W2 - W1 / W2 \times 100$$

Dissolution studies:[4]

In-vitro dissolution study is performed by using USP Type II Apparatus (Paddle type) at 50 rpm. Phosphate buffer pH 6.8, 900 ml is used as dissolution medium which is maintained at 37±0.5°C. Aliquots of dissolution medium (10 ml) are withdrawn at specific time intervals (2 min) and filter. An equal amount of fresh dissolution medium is replaced immediately following withdrawal of test sample. The percentage of drug released at various intervals is calculated. The values are given in Table 6 & Table 7, the drug release was depicted in the figures 6,7.8 & 9.

Table 6: Cumulative Drug Release Data of Frovatriptan Formulations Containing Various Diluents

Time	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
5	29.32	32.46	29.49	32.56	32.04	39.68	42.54	48.63
10	38.54	46.48	42.38	58.43	44.26	54.62	59.26	60.02
15	45.30	58.41	50.85	66.71	63.48	66.28	70.24	74.52
20	58.12	69.71	68.23	79.24	78.24	78.59	79.38	85.24
25	79.23	78.64	79.28	88.56	84.26	86.22	88.26	92.65
30	85.78	89.84	87.53	98.22	94.81	92.85	98.49	97.84
45	96.24	98.59	99.74	--	99.54	99.62	--	--
Time	F9	F10	F11	F12	F13	F14	F15	F16
0	0	0	0	0	0	0	0	0
5	32.58	38.26	42.86	44.02	32.64	39.24	42.03	46.64
10	45.86	56.48	59.32	62.86	40.86	52.06	54.36	59.82
15	59.90	68.26	70.29	76.28	58.22	68.64	69.84	72.46

20	73.51	87.42	86.24	84.06	72.38	79.29	76.02	83.22
25	88.08	92.36	96.42	99.64	84.29	84.22	86.46	95.84
30	96.02	99.62	--	--	92.33	99.64	96.25	--
45	--	--	--	--	98.25	--	--	--

Table 7: **Cumulative Drug Release Data Of Frovatriptan Formulations Containing Various Superdisintegrants**

TIME	F17	F18	F19	F20	F21	F22	F23	F24
0	0	0	0	0	0	0	0	0
5	14.62	17.25	22.48	26.21	30.28	38.26	42.26	9.26
10	21.28	29.41	35.41	39.42	42.24	54.92	58.84	19.48
15	30.28	36.42	43.26	52.26	56.34	68.26	69.28	31.26
20	36.42	42.28	59.21	60.86	69.72	77.28	80.92	45.21
25	49.54	56.86	67.24	69.24	81.26	86.42	92.36	56.28
30	70.26	68.42	78.26	82.42	89.42	96.21	98.02	68.24
35	79.85	79.21	84.26	90.56	96.21	--	--	74.68
40	86.02	89.98	92.86	96.28	--	--	--	86.21
45	95.82	96.52	98.92	--	--	--	--	95.42

F25	F26	F27	F28	F29	F30	F31	F32	F33
0	0	0	0	0	0	0	0	0
12.02	17.46	21.36	26.28	30.26	16.28	26.65	34.65	48.92
24.58	25.68	33.68	39.63	45.26	28.65	39.42	49.56	68.59
35.26	38.26	49.48	50.26	57.29	39.26	48.26	60.24	78.65
49.24	49.54	56.21	69.25	69.74	50.36	59.64	78.26	88.26
58.26	56.28	64.86	78.65	73.84	65.24	70.25	84.62	98.56
67.92	69.28	75.28	88.36	85.62	79.36	86.48	96.25	--
78.25	82.42	84.26	94.26	98.94	86.29	94.02	--	--
85.42	86.29	92.86	98.42	--	98.56	99.26	--	--
96.89	98.21	99.06	--	--	--	--	--	--

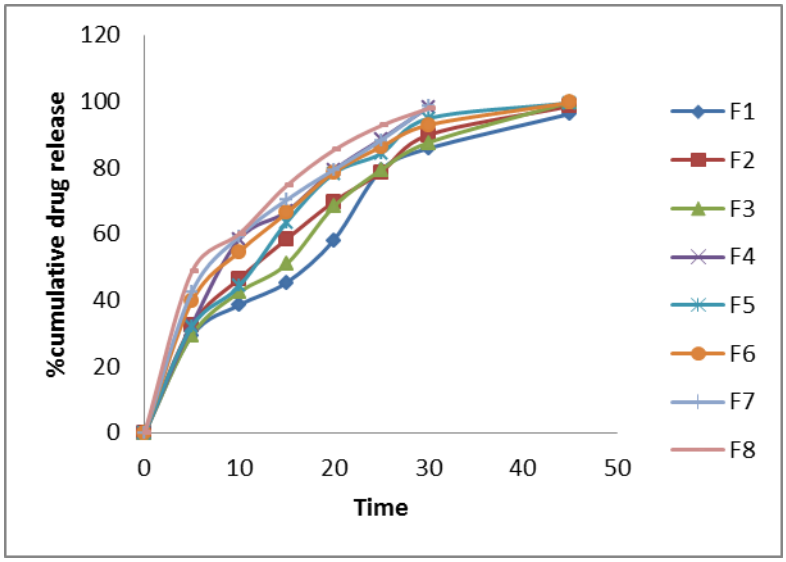


Figure 6: Drug release graph of Frovatriptan formulations containing various diluents F1-F8

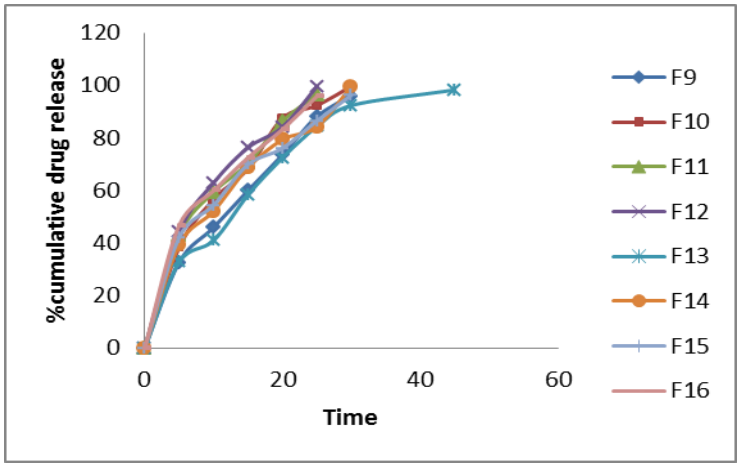


Figure 7: Drug release graphs of Frovatriptan formulations containing various diluents F9-F16

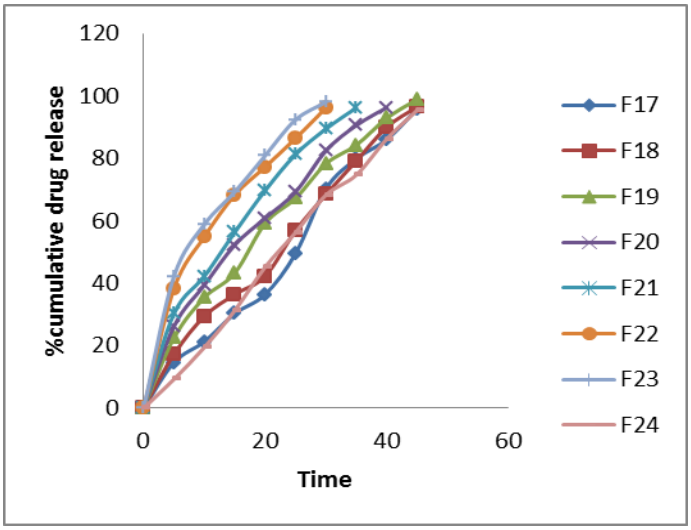


Figure 8: Drug release graphs of Frovatriptan tablets containing various superdisintegrants F17-F24

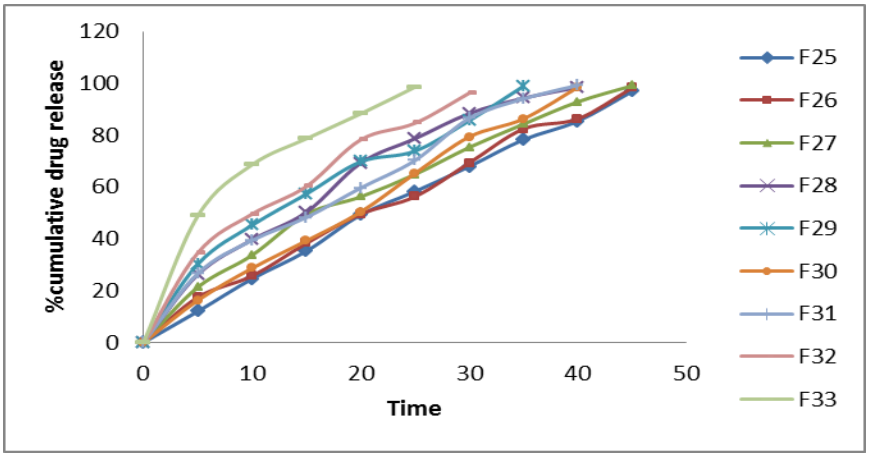


Figure 9: Drug release data of Frovatriptan formulations containing various superdisintegrants F25-F33

Factorial design:

Factorial design was constructed for the formulations which have shown the desired disintegration time and drug release to optimize the formulations. Design expert 10 software was employed to construct the factorial design. Statistical analysis was done by 2^2factorial design by employing design expert 10 software and the formulations were analysed for various parameters like ANOVA, half normal and normal plots, contour plot and overlay plot. The significance values 'p' were noted for the formulations containing various diluents and superdisintegrants separately and the optimized formulation was selected based on those values. Table 8 & fig 10,11,12.

Table 8 : Comparison of Best Formulation of Frovatriptan F33 With Marketed Product (Frova 2.5mg)

Time	F33	M.P
0	0	0
5	33.52	26.48
10	66.87	58.67
15	87.44	79.88
20	98.65	94.31

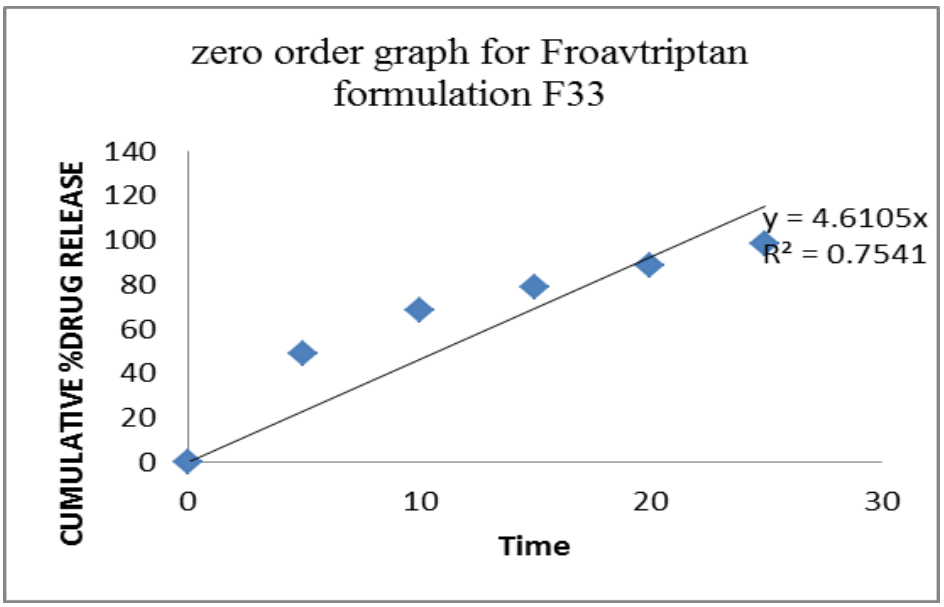


Figure 10: Graph of drug release kinetics of Frovatriptan best formulation

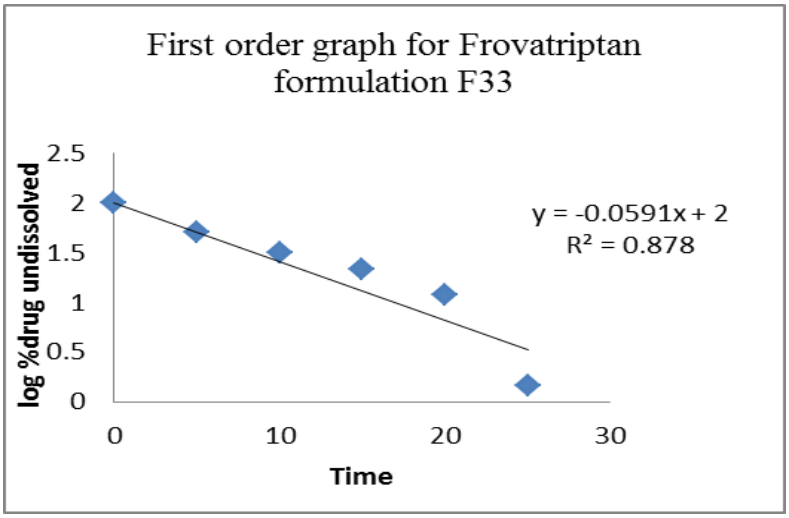


Figure 11: Graph of drug release kinetics of Frovatriptan best formulation

Stability studies:[5]

The selected formulation was packed in amber-colored bottles, which were tightly plugged with cotton and capped. They were then stored at 40^0C / 75 % RH for 3 months and evaluated for their physical appearance, drug content and in vitro dispersion time at specified intervals of time. The result is shown in Table 9.

RESULTS AND DISCUSSION:

Table 3: Calibration Curve Values Of Frovatriptan In 6.8 pH Phosphate Buffer

Conc	Abs
0	0
2	0.196
4	0.383
6	0.572
8	0.768
10	0.952
12	1.184

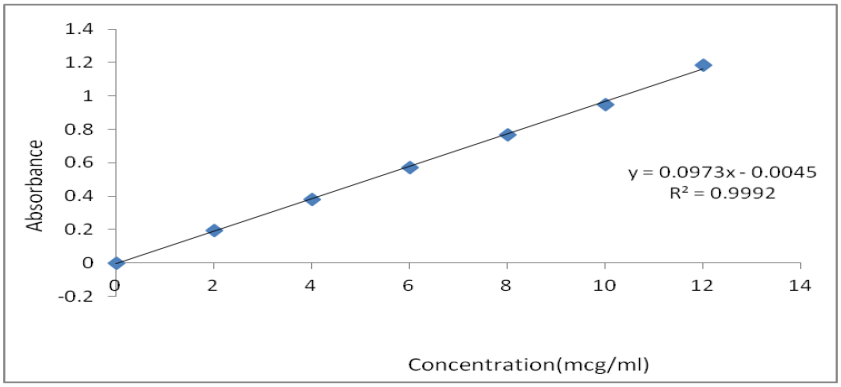


Figure 1: calibration graph of Frovatriptan pure drug

The standard calibration curve was constructed for Frovatriptan pure drug in pH 6.8 phosphate buffer by UV-spectophotophemeter and the maximum wavelength was found to be 224nm. The values were found to be linear and linearity is expressed by the value of correlation coefficient R^2= 0.9992.

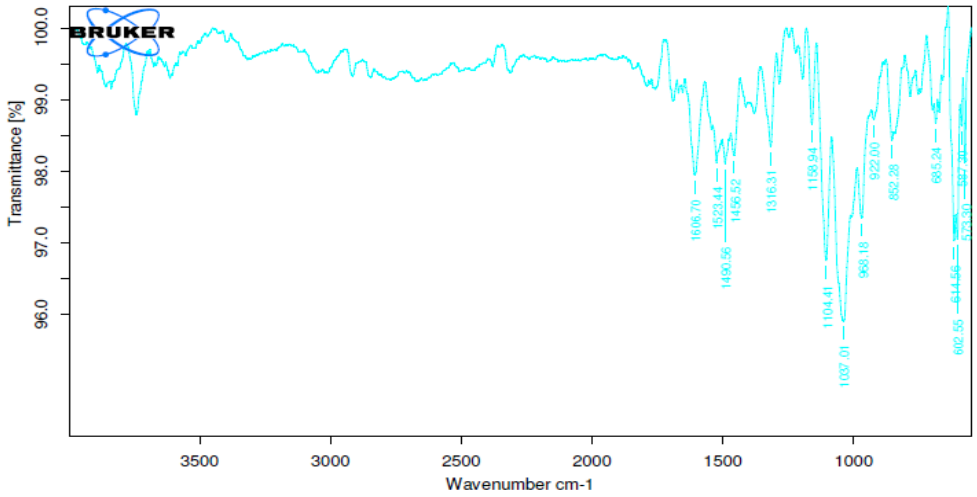


Figure 2: IR graph of Frovatriptan pure drug

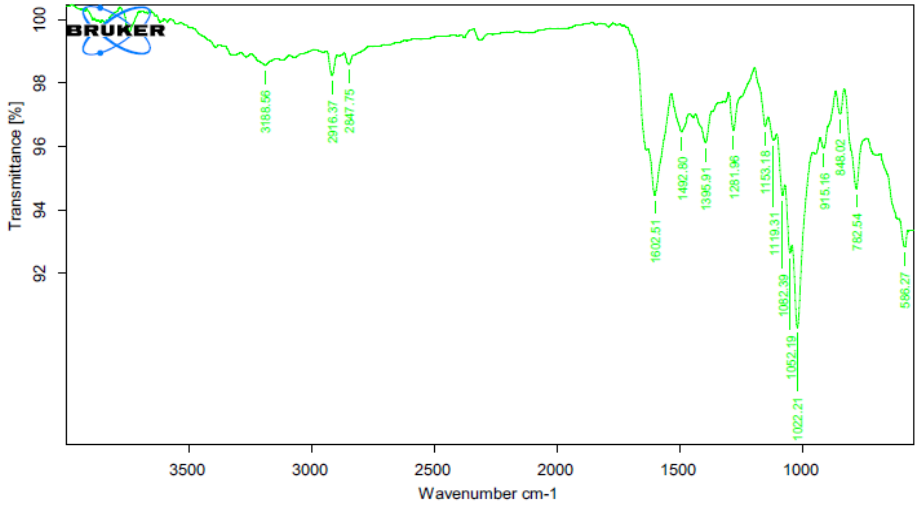


Figure 3: IR graph of best formulation of Frovatriptan Tablets

The peaks of various functional groups that were found in IR graphs of both pure drug and best formulation are found to be similar and there is no change in peaks it indicates that there is no interaction between the drug and the excipients employed and they are compatible with one another.

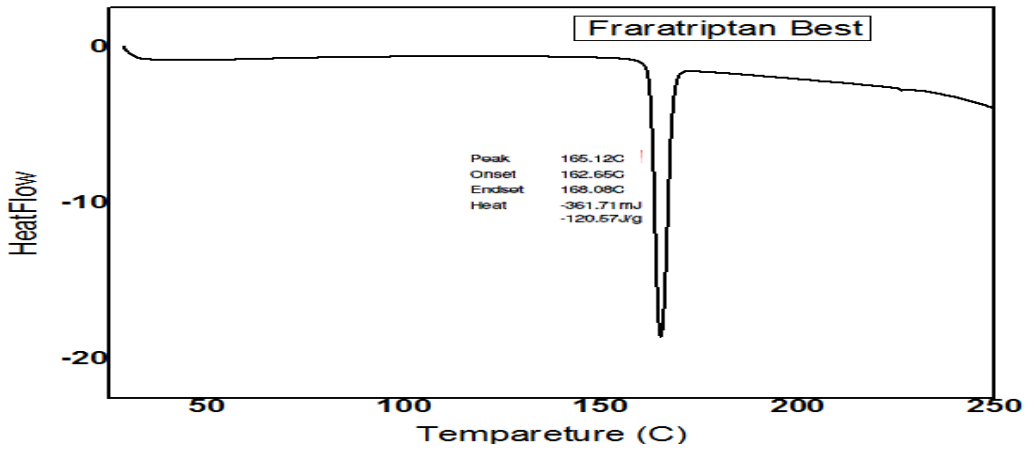


Figure 4: DSC graph of Frovatriptan pure drug.

DSC studies were conducted on pure drug of Frovatriptan between 50^0 to 200^0c and the sharp peak indicates that the drug taken is of desirable purity.

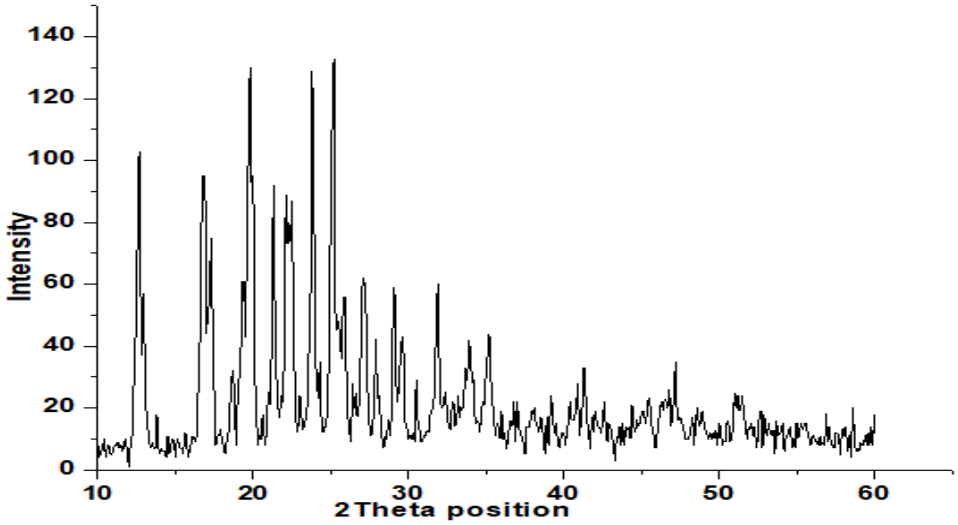


Figure 5: XRD studies on Frovatriptan drug

XRD studies were done on the Frovatriptan pure drug and the drug sample was found to be pure.

The angle of repose of different formulations was ≤ 29.09 which indicates that material had good flow property. So it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.31 g/cm^3 to 0.386 g/cm^3.Tapped density was found between 0.379 g/cm^3 to 0.463g/cm^3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 12.436 - 20.918 and Hausner's ratio from 1.14-1.26 which reveals that the blends have good flow character.

Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be ≤ 4.64 kg/cm^2. All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeial limits of the tablet weight. Friability values were found to be less than

1% in all the formulations F1 – F33 and considered to be satisfactory ensuring that all the formulations are mechanically stable. Disintegration values were found to be within 26 to 40 sec. The drug content uniformity was found between 92.82% - 99.24%. The wetting time was found to be between 18 – 30sec. The water absorption ratio was found in the range 0.176- 0.29sec. Thus the tablets were disintegrating rapidly within seconds and the wetting time and water absorption ratio were optimum for orodispersibility of tablets.

The cumulative drug release values were found for all the formulations with various diluents and the best formulation among these is F12 that contains Mannitol shows 99.64% drug release in 20min.This was taken for further study containing various superdisintegrants.

Formulation F12 has been selected for further study depending on the drug release and other 17 formulations were prepared using three different superdisintegrants in different concentrations. Among the above formulations F17 to F33, formulations F33 containing Cross povidone(5%) as superdisintegrant and Mannitol as diluent has shown best drug release of 98.56% in 25min.

The above graphs depict the cumulative drug release of various formulations F1 to F33. The first two graphs give the drug release of Frovatriptan formulations containing various diluents among which F12 was found to give best drug release.

The next two graphs give the drug release of various formulations of Frovatriptan containing various superdisintegrants and the formulation F33 was found to be the best and optimized formulation.

Drug kinetic studies were done on the best formulation and the best formulation F33 follows first order kinetics as the drug release depends on the concentration. The R^2 value for first order kinetics was found to be 0.878.

Table 9: ANOVA parameters of the selected formulation of Frovatriptan by factorial design

ANOVA for selected factorial model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	1348.358	1	1348.358	32.09304	0.029775	significant
B-CP	1348.358	1	1348.358	32.09304	0.029775	
Residual	84.0281	2	42.01405			
Cor Total	1432.387	3				
Std. Dev.	6.481825		R-Squared	0.941337		
Mean	73.795		Adj R-Squared	0.912005		
C.V. %	8.783555		Pred R-Squared	0.765348		
PRESS	336.1124		Adeq Precision	8.011621		
-2 Log Likelihood	23.53094		BIC	26.30352		
			AICc	39.53094		

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	73.795	1	3.240912	59.85048	87.73952	
B-CP	18.36	1	3.240912	4.41548	32.30452	1

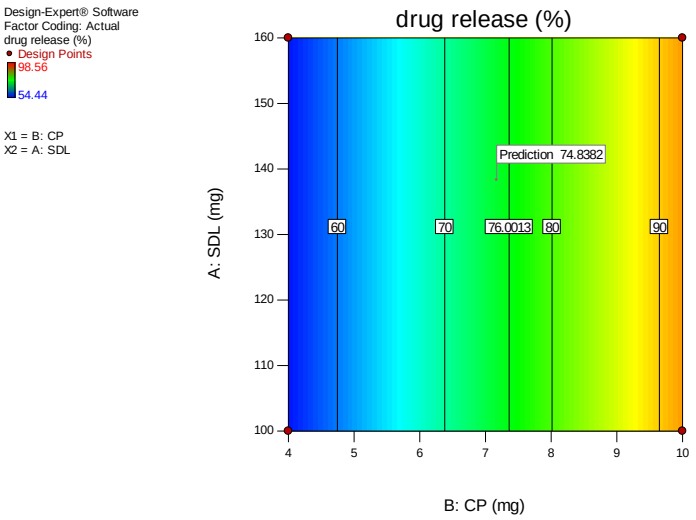
Final Equation in Terms of Coded Factors:

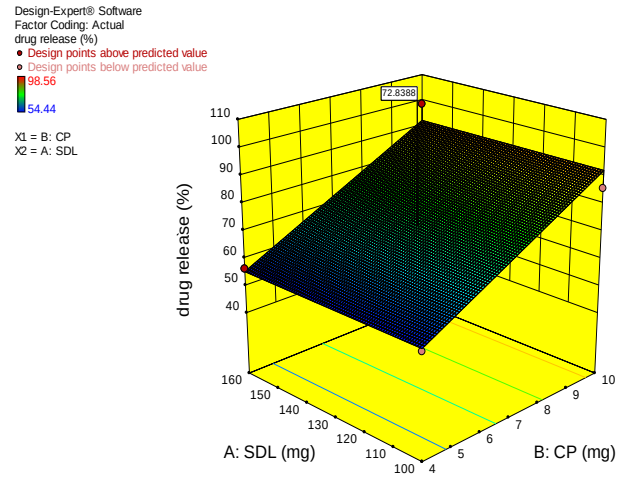
drug release = 73.795 18.36 * B

Final Equation in Terms of Actual Factors:

drug release = 30.955 6.12 * CP

The Model F-value of 32.09 implies the model is significant.





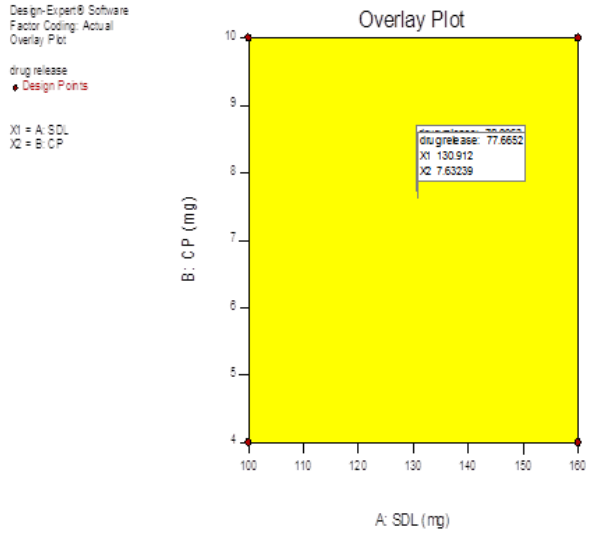


Figure 12,13 & 14: % drug release graph , overlay plot and 3-D surface graph of factorial design respectively

Table 10: Dissolution Studies Of Formulation F33 After 12weeks Of Stability Studies At 40^0 C /75% Rh

Time(mins)	Cumulative % drug release F33
5	33.51
10	66.84
15	88.34
20	98.95

The best formulation F33 was subjected to accelerated stability studies for 3 months. The drug release studies were conducted on the formulation after three months and there was no change in the drug release which shows that the formulation is stable.

ACKNOWLEDGEMENT:

We would like to thank JV Krishna Rao secretary JB educational society for giving us the opportunity to carry out the research work. Spectrum labs Hyderabad for providing the required chemicals and helping the research. Thanks to Dr.A. Srinivasa Rao principal Bhaskar pharmacy college for his constant support throughout the work. Thanks to Dr.T.E.G.K.Murthy principal Bapatla college of pharmacy for his valuable suggestions and his innovative ideas which helped in the progress of the work. Thanks to all the colleagues for trheir never ending spirit and confidence.

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