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FORMULATION AND CHARACTERIZATION OF FROVATRIPTAN SUCCINATE POROUS TABLETS BY SUBLIMATION TECHNIQUE

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ABSTRACT The main objective of this research work was to develop porous tablets of Frovatriptan Succinate by sublimation technique using camphor as sublimating agent and Sodium starch glycolate, Croscarmellose sodium and crospovidone as super disintegrating agents. The prepared formulations were subjected to evaluation for pre compression as well as post compressional parameters. The drug and excipients compatibility studies were done by FTIR studies. This demonstrated that there was no interaction between the drug and excipients. The pre compression parameters were within the prescribed limits and indicate good flow properties. In all the formulations post compressional parameter like hardness and friability were within the acceptable limits. Drug content was found to be high in FT6 formulation. The tablet thickness was between 2.4 to 2.6 mm. The weight variation results shows that average percentage deviation was less than 7.5%, which indicates good uniformity in all formulations. Disintegration time of the tablets was in the range of 2-6 mints. The FT6 formulations showed 50% of drug release in 10 mints and 90% drug release in approximately 20 mints. The FT6 formulation shows no significant changes during stability studies for 6 months.

KEYWORDS : Frovatriptan, Porous tablets, sublimation technique, SSG, Menthol.

INTRODUCTION:

The tablets and capsules are widely used oral dosage forms. Out of the two oral solid dosage forms the tablets are preferred dosage forms[1-2]. Even though the tablets are preferred dosage forms it suffers with certain disadvantages like difficulty in swallowing by the patients like paediatrics, geriatrics, bed ridden, mentally ill and disabled patients. There are some instances that patients suffer from sudden episodes of allergic attacks, all this contributes to patient non compliance and failure of treatment. To overcome all these problems the researchers are developed solid dosage forms (Tablets) that will disintegrate fastly or dissolve even when taken orally without water. Oral fast disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, rapid dissolving tablets and porous tablets. The concept of oral fact disintegrating tablets are relatively new technology that facilitates rapid disintegration or dissolution of the tablets with the help of super disintegrating agents like sodium starch glycolate, croscarmellose sodium and others[3-4].

The another approach in the formulation of oral fast disintegrating tablets are increasing the pore structure of the tablet matrix. Among the various techniques available for this the important techniques are freeze drying and vaccum drying. Among this these two vaccum drying is preferred by the many researchers as it is simple in operation when compared to freeze drying[5]. In vaccum drying sublimation of volatalizable ingradient is employed to increase the tablet porosity[6]. The main objectives of preparation of oral fast disintegrating tablets are to ensure rapid disintegration or increased dissolution in the saliva of oral cavity[7].

Frovatriptan Succinate chemically (methylamino)-2,3,4,9-tetrahydro-1H-carbazole-6-carboxamide. Frovatriptan is a second generation triptan 5-HT receptor agonist that binds with high affinity for 5-HT_{1B} and 5-HT_{1D} receptors. It is structurally distinct from, but pharmacologically related to other selective 5- HT1B/1D receptor agonists. Frovatriptan Succinate is believed to act on extra cerebral, intracranial arteries and to inhibit excessive dilation of these vessels in migraine. Research has shown that migraine can be caused by the swelling of blood vessels around the brain. Frovatriptan eases the pain associated with migraine by narrowing these blood vessels. The typical dose of Frovatriptan Succinate is 7.5 mg/day. It may be given twice / thrice daily. Tablet formulations containing 2.5 mg Frovatriptan Succinate is available in the market.

In the present research study, an attempt was made to formulate the porous tablets of Frovatriptan Succinate and to investigate the effect of sublimating agent on the release profile of drug in the tablets.

MATERIALS AND METHODS:

Frovatriptan Succinate was a gift sample from Mylan laboratories, Hyderabad. Croscarmellose Sodium, Crospovidone, Sodium Starch Glycolate, menthol, camphor, micro crystalline cellulose and all the other chemicals used were of pharmaceutical grade obtained from ESSEL Fine Chem., Mumbai.

Drug-Excipient Compatibility Studies:

The FTIR spectra of Frovatriptan Succinate along with other excipients were obtained by using Perkin Elmer FTIR spectro photometer, series 1600 which was calibrated with KBr dispersion method in the region between 400-4000 cm-1.

Preparation of Frovatriptan Succinate porous tablets:

Frovatriptan Succinate (2.5 mg) was thoroughly mixed with the superdisintegrants and then other exipients were added to the mixer and passed through the sieve (sieve no. 40). Collected the powder mixer, blended with magnesium stearate (pre sieved through sieve no. 60), then the blend was sent for tablet compression by using Round and flat faced punches in

CADMACH 16 punches tablet punching machine. Punches of 8 mm diameter were used for compression. Tablet of 200 mg was prepared by adjusting hardness and volume screw of compression machine properly. The tablets were dried for the sublimating agent to sublime (pore formation).

Table 1: Formulation Of Frovatriptan Succinate Porous Tablets.

Ingredients	FT1	FT2	FT3	FT4	FT5	FT6	FT7	FT8	FT9	FT10
Frovatriptan	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5mg
Menthol	20mg	20 mg	20 mg	20mg	20 mg	20 mg	20 mg	20 mg	20 mg	-
Camphor	-	-	-	-	-	-	-	-	-	20mg
MCC	163.5	153.5	143.5	163.5	153.5	143.5	163.5	153.5	143.5	143.5
SSG	10mg	20 mg	30 mg	-	-	-	-	-	-	-
CCS	-	-	-	10mg	20mg	30 mg	-	-	-	30mg
CP	-	-	-	-	-	-	10 mg	20 mg	30 mg	-
Mg.stearate	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4mg	4mg
Total weight	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg

Characterization Of Frovatriptan Succinate Porous Tablets:

The prepared tablets were evaluated for both pre-compressional parameters like bulk density, tapped density, hausners's ratio and compressibility index and as well as post-compressional parameters like weight variation, hardness, thickness, disintegration time, drug content and *in vitro* dissolution studies.

Weight variation:
Twenty tablets from each batch were weighed with electronic digital balance and average weight was determined. Then individual tablets were weighed and individual weight was compared with the average weight. The percentage deviation was calculated and checked for weight variation. Standard deviation was calculated. Using this procedure weight variation range of all the batches were determined and recorded.

Friability Test:
The friability test was performed for all the formulated Frovatriptan Succinate porous tablets. 20 tablets were taken and their weight was calculated. Later they were placed in the Roche friabilator and allowed to make 100 rotations. The tablets were then de-dusted and reweighed. The percentage weight loss was calculated. Percentage Friability was calculated as follows

$$\text{Friability (\%)} = w1\text{-}w2/w1 \times 100$$

Where w= Initial weight of 20 tablets. w2 = Final weight of 20 tablets after testing

Hardness test:
The tablet hardness of different formulations was measured using the Monsanto hardness tester for 6 tablets. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet, and a zero was taken. The upper plunger was then forced against the spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge on the barrel to indicate the force. The force of fracture is recorded and the zero force reading is deducted from it.

Thickness Of Tablets:
The thickness of individual tablets of 6 numbers were measured with vernier calipers, it permits accurate measurements and provides information of the variation between tablets. Tablet thickness should be controlled within ± 5% variation of standard value.

Drug Content:
Ten tablets were selected randomly and powdered. A quantity of this powder corresponding to one tablet was dissolved in 100 ml of 0.1N HCl, stirred for 15 min and filtered. 1 ml of the filtrate was diluted to 100 ml with 0.1N HCl. Absorbance of this solution was measured at 244nm using 0.1N HCl as blank and content of drug was estimated.

***In Vitro* Drug Release Studies:**
Dissolution of the tablet of each batch was carried out using USP type II apparatus (ELECTRO LAB) using paddles at 50 rpm. As per the official recommendation of IP 900ml of 0.1 N HCl used as dissolution medium and the temperature of the medium was set at 37 ± 0.5 0C. 5 ml of sample was withdrawn at predetermined time interval of 5min., 10min., 15min, 20min, 25min, 30min, 35min and 40min. And same volume of fresh medium was replaced.

The withdrawn samples were analyzed by an UV-visible spectrophotometer at 244 nm using buffer solution as blank solution.

Stability studies:
Frovatriptan tablets of F6 formulation were packed in HDPE (High density polyethylene) container with child resistant caps (CRC) and induction sealed.

These bottles were charged for stability study at 40±2oC, RH 75±5% for 3 months. At the end of 3rd month the formulation F6 was evaluated for its Physical Characteristics, Drug Content and Dissolution Properties.

Statistical analysis:
All experiments were repeated at least 3 times. Data are expressed as a mean ± standard deviation (SD, n = 3)

RESULTS AND DISCUSSION:
FTIR studies were performed to understand the compatibilities between the drugs with different excipients. The figures above illustrate that the functional groups like N-H with the observation range of 3350-3310 has peaks at 3322.29 in pure drug and 3321.97 in optimized formulation. Similarly the functional group C=O has a peak range of 1710-1685 has peaks at 1650.89 in pure drug and 1650.98 in optimized formulation.

The FTIR spectra of pure drug as well as optimized formulation were shown in Figure 1& 2, from the spectra it is evident that there was no interaction between the pure drug and excipients.

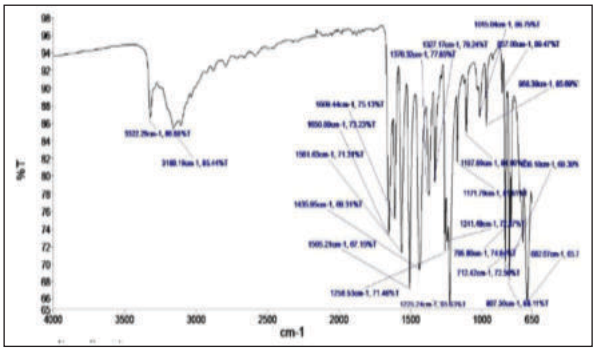

Figure 1: FTIR spectra of Pure Frovatriptan Succinate

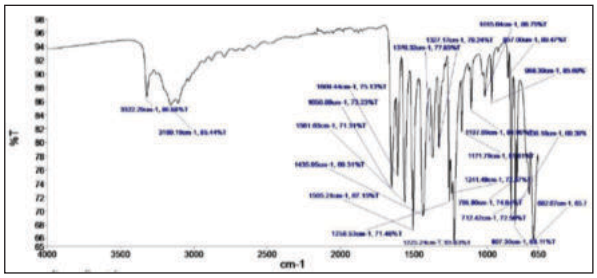

Figure 2: Ftir Spectra Of Frovatriptan Succinate Optimized Formulation F6

The flow properties of the powder blend was important for the uniformity of the drug in tablets. The blend was analyzed for parameters such as bulk density, tapped density, compressibility index and hausner ratio and the results were found to be within limits. The flow properties of the powder blend was good before compression.

After compression, all the tablets were dried at 60°C for 12 hrs and evaluated for post-compressional parameters like weight variation, hardness, thickness, friability, disintegration and *in vitro* drug release. The values of pre-compressional parameters as well as post-compressional parameters were shown in Table 2, 3 & 4

Table 2: Pre-compressional Parameters Of Frovatriptan Succinate Porous Tablets.

Formulation	Bulk Density (g/cc)	Tapped Density(g/cc)	Hausner ratio	Compressibility index (%)	Angle of repose	Flow properties
F1	0.464	0.574	1.23	19.1	29.47	Excellent
F2	0.423	0.501	1.16	15.5	27.63	Excellent
F3	0.456	0.542	1.22	15.8	25.54	Excellent
F4	0.467	0.559	1.25	16.4	26.23	Excellent
F5	0.485	0.593	1.10	18.2	27.21	Excellent
F6	0.460	0.556	1.21	17.2	30.38	Good
F7	0.478	0.575	1.24	16.8	28.46	Excellent
F8	0.450	0.554	1.28	18.7	25.71	Excellent
F9	0.442	0.537	1.27	17.6	31.82	Good
F10	0.467	0.559	1.25	16.4	26.23	Excellent

Table 3: Evaluation Of Post- Compressional Parameters Of Frovatriptan Porous Tablets Before Drying

Formulation	Hardness*[a] (kg/cm2)	Weight Variation*[b] (mg)	Thickness*[a] (mm)	Disintegration time[a] (min)	Drug Content*[c](%	Friability*
F1	6.0±0.17	201±0.59	2.4±0.05	6	98.2±0.62	0.58±0.05
F2	6.1±0.20	198±0.63	2.4±0.02	5min 24sec	98.72±0.23	0.50±0.05
F3	6.2±0.18	201±0.45	2.6±0.07	4min	98.4±0.34	0.52±0.05
F4	6.0±0.15	202±0.88	2.5±0.10	5min 45sec	98±0.56	0.33±0.05
F5	6.2±0.16	203±0.56	2.4±0.03	4min 34sec	98.44±0.49	0.31±0.03
F6	6.1±0.22	198±0.74	2.45±0.06	2min 21sec	100.8±0.27	0.46±0.05
F7	6.2±0.24	201±0.67	2.5±0.15	5min 32sec	98.2±0.63	0.45±0.04
F8	6.0±0.22	201±0.77	2.5±0.03	4min	98.4±0.56	0.49±0.01
F9	6.1±0.16	203±0.86	2.4±0.01	2 min 17sec	99.32±0.37	0.58±0.05
F10	6.1±0.12	198±0.54	2.4±0.05	2min 28sec	98±0.56	0.55±0.05

a = 6 tablets, b = 20, c=10 * Average of Three determinations

Table 4: Evaluation Of Post- Compressional Parameters Of Frovatriptan Porous Tablets After Drying

Formulation	Hardness*[a] (kg/cm2)	Weight Variation*[b] (mg)	Thickness*[a] (mm)	Disintegration Time[a] (sec)	Drug content*[c] (%)
F1	3.5.0±0.11	181±0.39	2.4±0.03	1min 14sec	98.2±0.62
F2	3.7±0.13	179±0.43	2.4±0.05	47sec	98.72±0.2
F3	3.9±0.15	182±0.47	2.6±0.06	38sec	98.4±0.34
F4	3.8±0.12	183±0.78	2.5±0.09	1min	98±0.56
F5	3.7±0.12	184±0.43	2.4±0.05	42sec	98.44±0.4
F6	3.6±0.19	183±0.51	2.45±0.08	18sec	100.8±0.27
F7	3.6±0.21	181±0.55	2.5±0.12	45sec	98.2±0.63
F8	3.9±0.25	183±0.57	2.5±0.06	28sec	98.4±0.56
F9	3.8±0.19	184±0.56	2.4±0.07	19sec	99.32±0.37
F10	3.7±0.16	183±0.31	2.4±0.08	22sec	98±0.56

a = 6 tablets, b= 20, c=10. * Average of Three determinations

The hardness of all the formulations was between 6.0 to 6.2 kg/cm^2, which indicates the good mechanical strength of the tablets. Tablet thickness was found to be 2.4 to 2.6 mm. The friability values were found to be less than 1% which indicates the good mechanical resistance. The weight variation results revealed that average percentage deviation of 20 tablets of each formulation was less than ± 7.5%, which provide good uniformity in all the formulations. Drug content was found to be high (≥ 100.8 %) and uniform in all formulations.

The disintegration time of all the formulations (F1-F10) were found to be in the range of 19-74 sec, which complies with official limits i.e. 3 mins.

The *in vitro* dissolution profiles of all the formulations were shown in fig.4 & 5. Out of the all the formulations F6 formulation shows faster drug release with in 18 sec.

The stability studies indicates that there was no significant changes in appearance, disintegration time and assay values in the optimized formulation F6 after 3 months stability studies.

CONCLUSION:

The drug release from the F6 formulation was fast in comparison to other formulations. It can be concluded that fast dissolving tablets with improved Frovatriptan Succinate dissolution could be achieved by sublimation of tablets containing suitable subliming agent.

Conflict Of Interest:

The authors have no conflict of interest in this research work.

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