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FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF FROVATRIPTAN

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ABSTRACT

Fast dissolving tablets were originally developed as novel drug delivery system to dissolve rapidly in mouth without the need of water, which provide instantaneous disintegration of tablet after putting on tongue, their by release the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach.The present research focuses on concept of development of Frovatriptan as fast dissolving tablets and various evaluation techniques. The aim of this study is to prepare fast dissolving tablets using Frovatriptan as a model drug for immediate disintegration and absorption and drug release characteristics in saliva. The formulation is based on preparation of fast dissolving tablets with three different superdisintegrants such as sodium starch glycolate, cross povidone and cross carmellose sodium used in different concentrations and formulated by different methods as wet granulation, direct compression and solvent evaporation techniques to get the desired release profile within minutes. The characterization studies were performed by conducting drug excipient compatibility studies by FT-IR. All formulations were evaluated for micromeritic properties, physical parameters like weight variation, hardness, friability, drug content etc., drug release & invitro drug release profile. It is concluded that the fast dissolving tablets of Frovatriptan were successfully formulated with superdisintegrants for immediate release and shows increased bioavailability and decreased first pass effect.

KEYWORDS: Frovatriptan, fast dissolving tablets, sodium starch glycolate, cross povidone, cross carmellose sodium.

INTRODUCTION[1]

Fast dissolving tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapimelts, porous tablets, quick dissolving etc. Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. The faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form. The basic approach in development of FDT is the use of superdisintegrants like cross linked carboxymethyl cellulose (croscarmellose), sodium starch glycolate (primogel, explotab), polyvinylpyrollidone (polyplasdone) etc, which provide instantaneous disintegration of tablet after putting on tongue, there by release the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. More ever, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablet. The technologies used for manufacturing fast-dissolving tablets are freeze-drying, spray-drying, tablet molding, sublimation, sugar-based excipients, tablet compression, and disintegration addition.

- **Christine walls et al[2];** published article on "pharmacokinetic profile of a new form of sumatriptan tablets in healthy volunteers" in *current medical and research opinion 2004 vol 20 No.6 pg. 803-809.*
- **R.V.Keny, Chrisma Desouza and C.F. Lourenco[3]** published article on "Formulation and evaluation of Rizatriptan Benzoate Mouth disintegrating tablets" in *Indian journal of pharmaceutical sciences .2010 Jan-feb; 72(1): 79-85.*
- **Piero Barbanti, Domenica le pera and Giorgio cruccu[4]** published article on "Sumatriptan fast-disintegrating / rapid-release tablets in the acute treatment of migrane" in *Expert review of neurotherapeutics in August 2007, vol.7, No.8, pg. 927-934.*
- **DJ yadav, M.M.nitalikar, v.v. more, D.A. chavan, s.s.suryawanshi[5]** published article on "Formulation and evaluation of fast dissolving tablets of Rizatriptan benzoate" with natural super disintegrants in *International journal of pharmaceutical research and development (IJPRD) 2011, vol4(7):sep 2012(007-013).*
- **Alpana.p.kulakarni, Amol b. khedkar, swaroop R.lahotib, M.H.D. Dehghanb[6]** published article on "Development of oral disintegrating tablet of Rizatriptan benzoate

with inhibited bitter taste" in *American-Eurasian journal of scientific research 7(2) : 47-57, 2012.*

- **The main objectives of the investigations are.**
- 1. The main objective of the investigation is to formulate and evaluate fast dissolving tablets of frovatriptan.
- 2. To study the drug and excepient compatibility by I.R spectral analysis.
- 3 .To prepare the tablet by wet granulation, direct compression and solvent evaporation techniques employing different excepients.
- 4. To evaluate the micromeretics parameters, angle of repose, bulk density, tapped density, cars index and Hauseners ratio.
- 5. To evaluate the parameters like % weight variation, hardness, % friability, drug content, wetting time.
- 6. To perform in-vitro drug release studies on the tablets and report % drug release & cumulative %drug release.

MATERIALS AND METHODS

MATERIALS

Pure drug Frovatriptan was a gift sample from Aurobindo Pharma limited, microcrystalline cellulose, Cross povidone, Sodium starch glycolate, Cross carmellose sodium were obtained from Qualigens chemicals, Mumbai. Magnesium stearate and talc was purchased from S.D.Fine Chem. Ltd, Mumbai. All other chemicals and reagents used were of analytical grade.

METHODS

Drug excipient Compatibility study

Compatibility of the drug with excipients was determined by FT-IR spectral analysis, this study was carried out to detect any changes on chemical constitution of the drug after combined it with the excipients. The samples were taken for FT-IR study.

Formulation methods

Wet granulation method

It involves main three steps weighing, Mixing, Granulation and Drying.

Weigh all the ingredients using electrical balance. mix Drug and superdisintigrant and add few drops of isopropyl alcohol. Then mix all the other ingredients. The obtained mass is

passed through sieve no. 16 .Dry the wet granules in a dryer for 30 minutes. In this way the granules are obtained.

Direct compression method

weigh all the ingredients using electrical balance. mix all the ingredients in a mortar and passed through sieve no.16. the obtained mixture is weighed according to tablet weight and subjected to direct compression.

Solvent evaporation

Drug and super disintegrants were mixed and to the mixture add few drops of methanol . then the solvent is allowed to evaporate. the evaporated mixture is mixed with other ingredients and weigh them according to the tablet weight & punch them .

Table 1: Formulation of fast dissolving Frovatriptan tablets by wet granulation method.

s.no	ingredients	f3(mg)	f6(mg)	f9(mg)
1	Frovatriptan	12.5	12.5	12.5
2	Cross povidone	12.5	-	-
3	Sodiumstarch glycolate	-	12.5	-
4	Crosscarmellose sodium	-	-	12.5
5	Pvp-k-30	10	10	10
6	Aerocil	1	1	1
7	Magnesium stearate	3	3	3
8	Aspertame	1	1	1
9	Citric acid	4	4	4
10	MCC	q.s	q.s	q.s
11	IPA	q.s	q.s	q.s
12	Lactose	155	155	155
13	Total weight	200	200	200

Table 2: Formulation of fast dissolving frovatriptan tablets by direct compression:

s.no	ingredients	f1(mg)	f4(mg)	f7(mg)
1	frovatriptan	12.5	12.5	12.5
2	cross povidone	12.5	-	-
3	sodium starch glycolate	-	12.5	-
4	crosscarmellose sodium	-	-	12.5
5	pvp-k-30	3	3	3
6	talc	1	1	1
7	magnesium stearate	3	3	3
8	citric acid	2	2	2
9	aspertame	1	1	1
10	lactose	163	163	163
11	total weight	200	200	200

Table 3: Formulation of fast dissolving Frovatriptan tablets by solvent evaporation method.

s.no	ingredients	f2(mg)	f5(mg)	f8(mg)
1	frovatriptan	12.5	12.5	12.5
2	cross povidone	12.5	-	-
3	sodium starch glycolate	-	12.5	-
4	crosscarmellose sodium	-	-	12.5
5	pvp-k-30	3	3	3
6	magnesium stearate	3	3	3
7	talc	3	3	3
8	citric acid	1	1	1
9	lactose	165	165	165
10	m ethanol	q.s	q.s	q.s
11	total weight	200	200	200

Micromeritic studies[7]

Bulk Density (Db)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the known weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml

$$D_b = M / V_b$$

Where :, M is the mass of powder; Vb is the bulk volume of the powder.

Tapped Density

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by.

$$dt = m / vt$$

where, m is the mass of powder ; vt is the tapped volume of the powder.

Angle of repose (θ)

It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane. It was determined by fixed funnel method and can be caluculated by the formula.

tan (θ) = h / r

θ = tan-1 (h / r)

where, θ is the angle of repose; h is the height in cms ; r is the radius in cms.

Carr's consolidation Index

This property is also known as compressibility. It is indirectly related to the relative flow rate, cohesiveness and particle size. It was calculated by using following formula.

$$\text{Consolidation Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \text{ X } 100$$

Haussner ratio(I)

haussner ratio is an indirect index of ease of powder flow. it is calculated by the following formula.

$$I = dt/db$$

dt is the tapped density; db is the bulk density.

Evaluation of fast dissolving tablets[8]

Weight variation

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. weight variation specification as per i.p average weight of tablet % deviation is 80 mg or less ±10 more than 80 mg but less than 250 mg ±7.5 250 mg or more ±5.

Hardness

Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric compression was measured using monsanto tablet hardness tester. it is expressed in kg/cm.[2]

Friability (f)

friability of the tablet determined using roche friabilator. this device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at i height of 6 inches in each revolution. preweighted sample of tablets was placed in

the friabilator and were subjected to the 100 revolutions. tablets were dusted using a soft muslin cloth and reweighed. the friability (f) is given by the formula.

$$f = \left[\frac{W_{(initial)} - W_{(final)}}{W_{(initial)}} \right] X\ 100$$

Wetting time[9]

Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. ten millimeters of water-containing eosin, a water-soluble dye, is added to petridish. a tablet is carefully placed on the surface of the tissue paper. the time required for water to reach upper surface of the tablet is noted as a wetting time.

Drug content determination

For determination of the drug content, a total 10 tablets were weighed and powdered. the powder equivalent to 12.5mg of frovatriptan was weighed and dissolved in phosphate buffer 6.8 :methanol(1:1) and then filtered through watt man filter paper and analyzed the drug content by measuring the absorbance at 231nm.

***In- vitro* dissolution studies**[10]

in-vitro drug release is carried out using usp tdt-08l (lab india, mumbai) employing paddle method .the dissolution was performed in phosphate buffer ph 6.8 as a dissolution medium (500ml) and the temperature was maintained at 37±0.5^{0}c. The speed of the paddle was adjusted at 50 rpm. an aliquot of 5ml sample was withdrawn at every five minutes. the replaced samples were refreshed with fresh medium. samples withdrawn were filtered through what mann filter paper and analyzed at 231nm using uv–visible double beam spectrophotometer.

RESULTS AND DISCUSSION

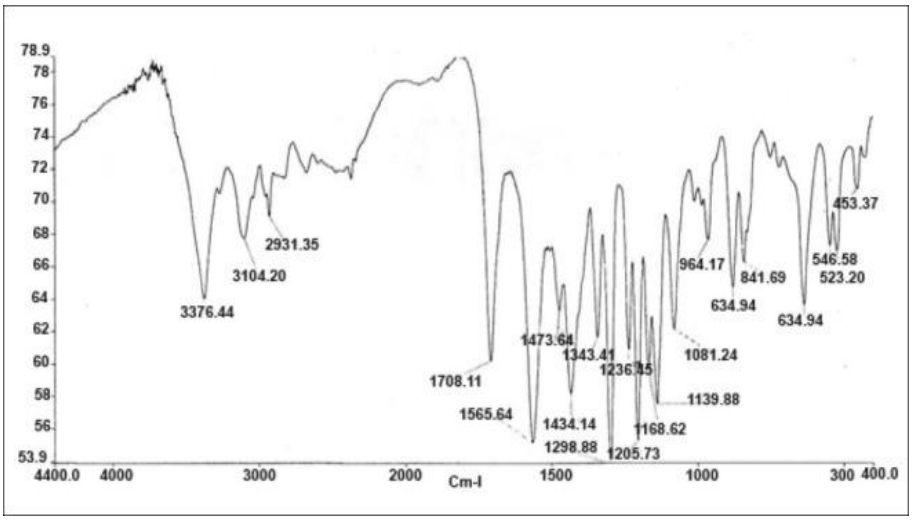

Fig 1: IR graph of Frovatriptan pure drug.

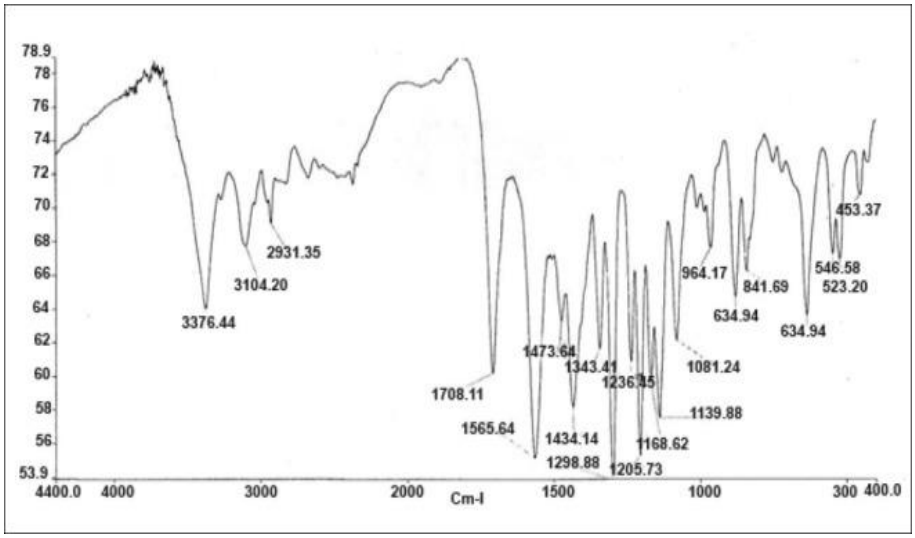

Fig 2: IR graph of best formulation.

The IR spectra of frovatriptan and best formulation was shown in Fig 1, Fig 2. The following principle peaks were observed.

1. C=O ---- 3376
2. O-H (Stretching) ---- 3104
3. C-H (Stretching) ---- 2931
4. C-H (Bending) ---- 1434
5. O-H (Bending) ---- 1205

The peaks observed in the individual IR graphs of the drug and excipients were also found in the formulation. Thus the studies revealed that no interaction exists in between frovatriptan and the excipients employed.

Table 4: Micromeritic properties of the blends containing, Frovatriptan and the selected excipients.

Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Haussner's ratio	Angle of repose (°)
F1	0.264	0.3	28	1.38	28.59
F2	0.26	0.28	31.1	1.5	30.79
F3	0.266	0.29	33.35	1.50	21.80
F4	0.36	0.404	12.22	1.12	26.56
F5	0.35	0.376	7.69	1.07	28.59
F6	0.463	0.51	10	1.10	26.56
F7	0.367	0.396	7.94	1.07	27.64
F8	0.396	0.457	15.60	1.15	30.96
F9	0.429	0.490	14.33	1.14	28.81

The physical mixtures of the formulation F_1, F_2, F_3, F_4, F_5, F_6, F_7, F_8, F_9 evaluated for bulk density, tapped density, Carr's index, haussner's ratio and angle of repose. The results were reported in Table 4..

The bulk density of three formulations F_1, F_2, F_3 by using wet granulation method was found to be 0.264, 0.260, 0.266 gm/ml. The tapped density was found to be 0.3, 0.288, 0.299 gm/ml. The Carr's index was found to be 28, 31.1, 33.35. The haussner's ratio was found to be 1.38, 1.5, 1.50. The angle of repose was found to be 28.59, 30.79, 21.80 respectively. The bulk density of three formulations F_4, F_5, F_6 by using direct compression method was found to be 0.36, 0.35, 0.463 gm/ml. The tapped density was found to be 0.404, 0.376, 0.51 gm/ml. The Carr's index was found to be 12.22, 7.69, 10. The haussner's ratio was found to be 1.12, 1.07, 1.10. The angle of repose was found to be 26.56, 28.59, 26.56. respectively. The bulk density of three formulations F_7, F_8, F_9 by using solvent evaporation method was found to be 0.367, 0.396, 0.429 gm/ml. The tapped density was found to be 0.396, 0.457, 0.490 gm/ml. The Carr's index was found to be 7.94, 15.60, 14.33. The haussner's ratio was found to be 1.07, 1.15, 1.14. The angle of repose was found to be 27.64, 30.96, 28.81 respectively.

Table 5: Physical parameters of Frovatriptan tablets formulated with various excipients by different methods:

Formulation code	Average weight (mg±S.D)	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)
F1	202±0.045	3.4	0.262	92.81
F2	200±0.036	3.0	0.259	96.55
F3	200±0.04	3.8	0.25	91..42
F4	199±0.59	4.1	0.40	94.31
F5	198±0.050	3.6	0.306	95.78
F6	201±0.032	4.2	0.50	94.01
F7	197±0.02	3.4	0.202	97.25
F8	200±0.323	3.7	0.265	94.60
F9	202±0.29	3.7	0.244	96.37

The results of physico-chemical evaluation of tablets were resulted in Table 5. The % weight variation and hardness of the tablets using wet granulation method was in the range of 205±0.045 to 200±0.036mg and 3.8 to 3.0 kg/cm. The % friability and the % drug content was found to be in the range of 0.262 to 0.25% and 96.55 to 91.42%. The % weight variation and hardness of the tablets using direct compression method was in the range of 511±0.59 to 506±0.050 mg and 4.2 to 3.6 kg/cm. The % friability and the % drug content was found to be in the range of 0.50 to 0.306% and 95.78 to 94.01%. The % weight variation and hardness of the tablets using wet granulation method was in the range of 201±0.29 to 199±0.323 mg and 3.7 to 3.4 kg/cm. The % friability and the % drug content was found to be in the range of 0.265 to 0.202% and 97.25 to 94.60%.

Table 6: In vitro dissolution data of frovatriptan tablets formulated by different super disintegrants using different methods.

S. No.	Time (Min)	Percent drug dissolved ($\bar{x}$ ± S.D.)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	2	9.121	9.991	8.369	5.266	6.535	8.181	7.235	8.546	6.548
3	4	23.610	27.198	22.986	18.148	20.607	22.609	21.546	22.331	21.564
4	6	39.239	43.054	37.808	31.349	37.766	44.878	38.655	38.448	39.522
5	8	46.037	50.343	46.714	41.160	48.553	56.644	47.554	49.554	45.552
6	10	54.281	59.786	55.668	51.259	58.457	67.769	57.771	62.442	59.321
7	12	63.276	70.221	66.080	62.589	70.061	80.129	63.254	75.263	72.543
8	15	73.729	80.242	76.079	74.450	85.019	92.555	74.522	87.356	90.682

The in-vitro drug release studies were conducted on all the formulations and the % drug release for 15 min was found to be 73.729%, 80.242%, 76.079%, 74.450%, 85.019%, 92.555%, 74.522%, 87.356% and 90.682% respectively.as shown in table 6. Hence the

formulation containing SSG and drug in 1:1 ratio formulated by wet granulation is considered as best formulation as shown in fig 3.

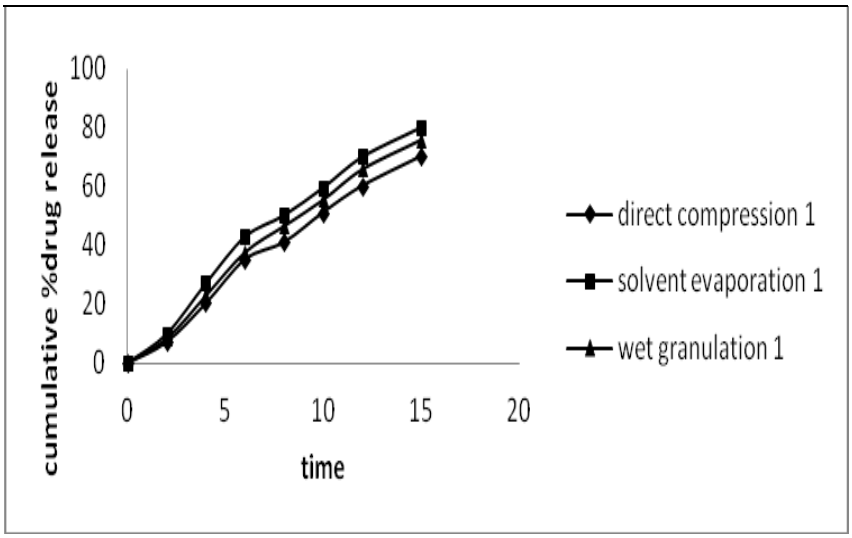

Fig 3: Drug release pattern of Frovatriptan tablets containing SSG as superdisintegrant

CONCLUSION

The objective of the study was to formulate and evaluate the tablets of frovatriptan. The fast dissolving tablets of Frovatriptan were successfully prepared with super disintegrants (cross povidone, cross carmellose sodium, sodium starch glycolate), PVP-K-30, Magnesium stearate, talc, lactose, MCC, Citric acid and aspartame by direct compression, wet granulation and solvent evaporation techniques of which wet granulation was found to be the best method. The physical mixtures and granules were subjected to determine the micromeritic properties and the formulated tablets were evaluated for various physical parameters and also evaluation tests were conducted on them.

The micromeritic properties evaluated such as bulk density, tapped density, angle of repose(θ), carr's index and Hausener's ratio were found to be within in the limits for both the powder mixtures and granules as shown in table 4 and it states that they are suitable to formulate the tablets by direct compression method and will have free flow from hopper into the die cavity.

The physical parameters evaluated such as weight variation , hardness, friability, drug content uniformity were also found to be within the limits of I.P. were shown in table 5.

The tablets that were formulated by wet granulation technique have shown more %drug release in 15 min compared to tablets formulated by other methods shown in table 6. The

formulation F6 was found to be best formulation containing sodium starch glycolate in 1:1 ratio to drug which shows a release of 92.555% in 15min.

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