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FORMULATION AND EVALUATION OF FAST DISSOLVING THIN ORAL FILMS OF FROVATRIPTAN

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Abstract:

In the present research work Frovatriptan drug was formulated as Fast dissolving Thin oral films by solvent casting method. Triptans are a class of anti migraine drugs which are formulated to give rapid relief from migraine attacks. Previously prepared in the form of tablets which has certain disadvantages so are formulated as films which disintegrate rapidly within in seconds in the mouth without need of water. The films were prepared by employing Frovatriptan drug, Hydroxy Proipyl Methyl Cellulose (HPMC E5) as polymer, Isopropyl alcohol was employed as solvent, Propylene glycol as plasticizer, Mannitol as diluents and aspartame as sweetening agent. The films were evaluated for parameters like Weight uniformity, Morphological properties Thickness uniformity, Folding endurance, Surface pH, Drug content uniformity test, In-vitro disintegration test, In-vitro dissolution studies which were found to be satisfactory. Among all the formulations F8 has found to be the best formulation with a disintegration time of 12sec and 100% of cumulative drug release within in 20min. Thus it indicates that Frovatriptan is highly suitable to be formulated as Fast dissolving thin oral films for their rapid release and immediate treatment of migraine attack.

Keywords: *Frovatriptan, HPMC E5, Maltodextrin, Mannitol, Propylene glycol, Aspartame.*

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INTRODUCTION [1,2]:

Fast dissolving technology have been emerges out as a new drug delivery system that provides a very convenient means of taking medications and supplements for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. Oral mucosa has a rich vascularization and offers higher permeability to many drugs. It has been well known that after buccal and sublingual administration drug solutes are rapidly absorbed in to the reticulated vein and are then drained into the systemic circulation. The films that are prepared have several advantages of avoiding dysphagia and first pass metabolism of drugs so that the bioavailability of drug gets enhanced. Migraine is a disorder which is caused due to vasodilatation of intra cranial arteries and causes severe headache that lasts from 2hrs – 72hrs. Thus the medications that are to be selected should give rapid relief from such a pain. The triptans are novel drugs in the treatment of migraine that act as 5-HT receptor agonists and cause vasoconstriction of intra cranial arteries and thus decrease the pain of migraine attack. Thus they are formulated as fast dissolving tablets, sublingual tablets and oral films to show raipd release from the oral cavity into the systemic circulation to give rapid relief from the migraine attack. Among which films have a larger surface area and are more rapidly disintegrated and dissolve for absorption in oral cavity.

MATERIALS AND METHODS:

Frovatriptan was obtained as a gift sample from Pharmatrain, Hyderabad. Maltodextrin was obtained from SD Fine chemicals, Mumbai, Mannitol was obtained from Metro chemicals, Hyd, HPMC E5, Propylene glycol, aspartame were obtained from Nihal pharma Hyd. All the chemicals obtained are of laboratory grade.

Calibration curve of Frovatriptan in 6.8pH phosphate buffer solution [3]:

A standard stock solution of Frovatriptan was prepared by dissolving accurately weighed 10mg of Frovatriptan in 6.8pH phosphate buffer solution in a 100ml volumetric flask and the volume was made up to 100ml by using 6.8pH phosphate buffer solution to obtain a stock solution of 100µg/ml. From the standard stock solution, 1 ml was taken into 10ml volumetric flask. The volume was made up to 10ml with 6.8pH phosphate buffer solution. The resulting solution containing 10µg/ml was scanned between 200 and 400nm. The λmax was found to be 229nm and was used as analytical wavelength. From stock solution, appropriate aliquots were pipetted into different volumetric flasks and volumes were made up to 10 ml with 6.8pH phosphate buffer solution so as to get drug concentrations of 1,2,3,4 and 5µg/ml. The absorbences of these drug solutions were estimated at λmax 229nm against a blank of 6.8pH phosphate buffer solution. This procedure was performed in triplicate to validate the calibration curve.

Drug- Excipient compatibility studies [3]:

The infrared absorption spectra of pure drug, pure polymer and physical mixture of polymer and drug were performed for polymer drug interaction studies between 4000 $cm^{-1}$to 400 $cm^{-1}$by KBr pellet method.

Formulation of Frovatriptan disintegrating films:

Preparation of mouth dissolving film by solvent casting method:

The mouth dissolving films of Frovatriptan using polymers were prepared by solvent casting method. A solution of the polymers was prepared in Isopropyl alchol. Frovatriptan was added to the aqueous polymeric solution. This was followed by addition of plasticizer Propylene glycol. Sweetener aspartame and pipperment flavours were also added to the above solution. The solution was casted on a petridish (diameter 6.5 cm) and dried at room temperature for 24 hr. The film was carefully removed from the petridish, checked for any imperfections and cut into the required size to deliver the equivalent dose (2 x 2 cm^{2}) per strip. The samples were stored in a dessicator at relative humidity 30-35 % until further analysis.

Table 1: Formulation table of Frovatriptan mouth dissolving films:

S.NO	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1.	Frovatriptan	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
2.	Hpmc E5 Cps	30	35	40	40	20	15	20	30
3.	Maltodextrin	10	10	10	-	20	20	10	-
4.	PG	8	8	10	8	8	6	6	6
5.	mannitol	31.5	26.5	19.5	31.5	31.5	38.5	43.5	43.5
6.	Aspartame	5	5	5	5	5	5	5	5
7.	PipermentFlavour	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
	Total	87.5	87.5	87.5	87.5	87.5	87.5	87.5	87.5

Evaluation of Oral disintegrating films [4,5]:

Weight uniformity of films:

Three films of each formulation trial of 2cm*2cm size were taken and weighed individually in electronic balance and the average weights were calculated. The results were summarized in results part.

Morphological properties:

This parameter was checked simply with visual inspection for physical appearance of films and evaluation of texture by feel or touch.

Thickness uniformity:

All the eight batches were evaluated for thickness by using calibrated Vernier caliper with a least count of 0.01mm. The thickness was measured at three different spots of the films and the average was taken. The results were summarized in results part.

Folding endurance:

The folding endurance was measured manually for the prepared films. The flexibility of films can be measured quantitatively in terms of folding endurance. A strip of film was cut (approximately 2*2cm) and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. The results were summarized in results part.

Surface pH:

Surface pH was found out by placing the film on the surface of 1ml of distilled water. The surface pH was noted by bringing pH paper near the surface of the films and allowing it to equilibrate for 1min. The change in the color of pH paper was observed.

Drug content uniformity test:

Drug content uniformity of all eight batches was determined by UV-Spectrophotometric method. For this, each strip at three different places equivalent to 2.5mg of drug was cut and dissolved in 50ml of 6.8pH phosphate buffer solution with continuous stirring. This solution was filtered using Whattmann filter paper, and the filtrate was diluted to 100ml with the same buffer in a volumetric flask. This solution was analyzed by U.V.Spectrophotometer and the absorbance was recorded at 229nm. Drug content was calculated by using calibration curve of drug. The results were summarized in results part.

In-vitro disintegration test:

In vitro disintegration time is determined visually in a glass dish of 25ml distilled water with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates. The results were summarized in results part.

***In vitro* dissolution studies [6]:**

The in vitro dissolution test was performed in USPI (basket) dissolution apparatus. The dissolution medium consisted of 900 mL 6.8pH phosphate buffer solution, maintained at 37±0.5°C and stirred at 50 rpm. One film was used in each test. Samples of dissolution medium (5ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and drug release was analyzed spectrophotometrically at 229nm. The volume withdrawn at each interval was replaced with freshly quantity of dissolution medium. Cumulative percent drug release of frovatriptan was calculated and plotted against time.

Stability studies:

The stability study was performed for formulation F8, as it was the optimized formulation based on results of the evaluation parameters. An accelerated stability study were performed for formulation F8 by storing at temperature 400C / 75%RH as per ICH guidelines and was studied for 30 days. The morphological properties of the formulation were smooth and elegant, indicating no change in physical stability. The drug content, disintegration time and % drug release was analyzed. From the data it was observed dosage form was stable.

RESULTS:

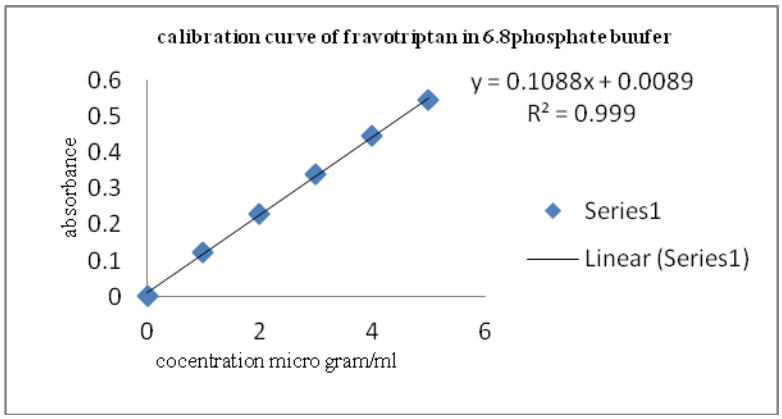

Fig 1: Calibration curve of Frovatriptan pure drug

Table 2: Precompression parameters evaluation for Frovatriptan mouth dissolving films

Formulation code	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Disint.Time	28sec	22sec	19sec	14sec	20	15	15	12
Appearance	film is smooth and clear	film is smooth and clear	film is smooth and clear	film is smooth and clear	slightly hazy	slightly hazy	smooth n clear film	smooth n clear film
folding endurance	20	18	17	15	19	22	17	17
thickness	0.142mm	0.145mm	0.142mm	0.146mm	0.143mm	0.141mm	0.144mm	0.146mm
Weight variation	87.5	87.1	88	85.3	84.2	87	86.3	85.2
content uniformity	98	98.5	99.6	99	98.5	99	98.1	98.9

Table 3: Cumulative drug release values of mouth dissolving films of Frovatriptan

Time in min	**% Cumulative drug release(%CDR)**							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0	0	0	0	**0**	0	0	0	**0**
5	54	51	48	**65**	55	62	65	**68**
10	68	59	55	**81**	67	75	76	**85**
15	79	69	71	**92**	84	87	90	**93**
20	89	87	86	**98**	93	94	94	**100**
30	94	91	92	-	96	97	96	

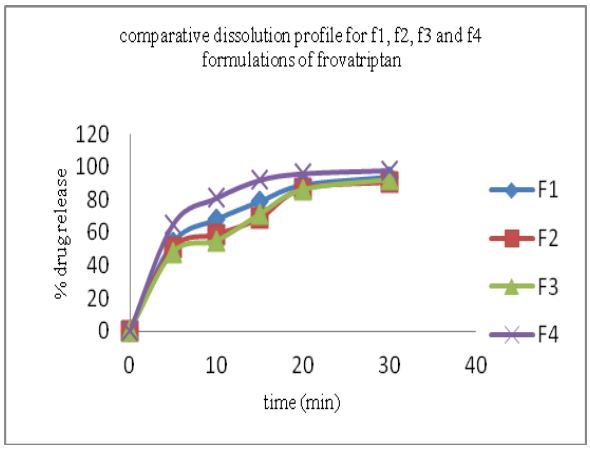

Fig 2: cumulative drug release profile for F1, F2, F3 & F4 formulations of Frovatriptan

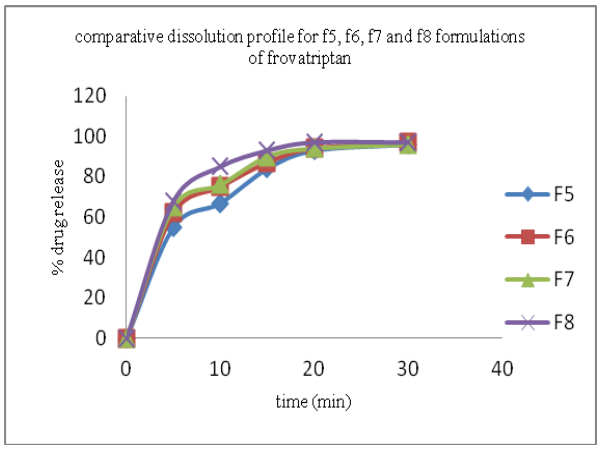

Fig 3: cumulative drug release profile for F5, F6, F7 & F8 formulations of Frovatriptan

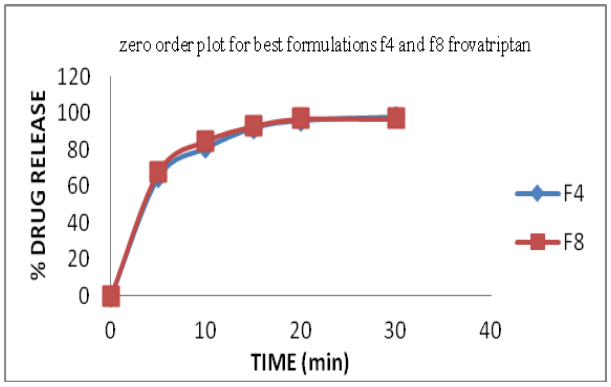

Fig 4: Zero order plots of best formulations F4 and F8

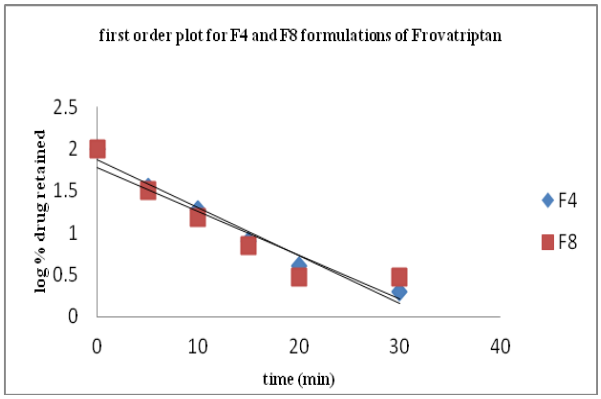

Fig 5: First order plots of best formulations F4 and F8

Table 4: Stability data of best formulation of Frovatriptan

Time in months	Formulation F8 stored at 40°C / 75% RH			
	Physical appearance	Drug content (%)	Disintegration time in sec	% Drug release
Intial	Smooth & elegant	99.86±0.05	12	98.01
After 30days	Smooth & elegant	98.53±0.18	14	97.41

DISCUSSION:

The weights of the films were found to be in the range of 85.2 to 88 mg. The thicknesses of the films were in the range of 141 µm to 146µm. Folding endurance of the films was found to be in the range of 15 to 22. The surface pHs of all the films were found to be neutral as there was no colour change in the litmus paper. The drug content uniformity is performed by taking three films in each formulation trial and the average drug content was calculated. The disintegration time of the prepared films were in the range of 12sec to 28sec. All the results were summarized in the table 2. The in-vitro drug release study of Frovatriptan FDF from each formulation was carried out in 6.8pH phosphate buffer solution for 30min. the drug release was found to be in the range of 91.00 to 100.00%.

CONCLUSION:

In-vitro drug release study result shows that as the concentration of plasticizer increases, drug release of mouth dissolving films also decreases and films are flexible at certain concentrations beyond that films are brittle, so concentration of the plasticizer was kept constant. In-vitro drug release study results shows that as the concentration of polymer increases, drug release of mouth dissolving films decreases. All the formulations showing optimum disintegration time, folding endurance, content uniformity and thickness Frovatriptan oral soluble films can be prepared successfully by employing F8 formulation in which Hpmc E5(30mg) and propylene glycol (6mg), mannitol (43.5mg) aspartame (5mg), peppermint flavor(0.5mg) was used and prepared in solvent casting method has shown better physico chemical characteristics and drug release kinetics and stability.

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