FORMULATION & *IN-VITRO* EVALUATION OF SUSTAINED RELEASE TABLETS OF FROVATRIPTAN FOR THE TREATMENT OF MIGRAINE

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ABSTRACT:

Frovatriptan is a Triptan drug created by Vernalis for the treatment of headache migraines, specifically those related with period. Frovatriptan causes vasoconstriction of conduits and veins that supply blood to the head. Current research is about formulation and evaluation of frovatriptan Sustained Release tablets, F8 with 97.09% is the best formulation. **Aim & Objective:** Formulating Frovatriptan Sustained Release Tablets using various natural polymers. To study the effect of Drug polymer ratio or concentration of polymer on drug release. To study the effect of pre formulation studies on release of drug from tablet. To determine the kinetics and mechanism of drug release. **Methodology:** Analytical method development. Drug – Excipient compatibility studies. Preformulation parameters. Evaluation of post compression parameters for prepared Tablets. In vitro drug release studies. **Results & Discussion:** The present study was aimed to developing Sustained Release tablets of Frovatriptan using various natural polymers. All the formulations were evaluated for physicochemical properties and In-vitro drug release studies. **Conclusion:** The aim of the present study was to develop Sustained Release Tablet formulation of Frovatriptan to maintain constant therapeutic levels of the drug for over 12 hrs. Xanthan gum, Guar gum and Karaya gum were employed as polymers. Frovatriptan dose was fixed as 2.5 mg. Total weight of the tablet was considered as 60 mg. Polymers were used in the concentration of 5 mg, 10 mg and 15 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation F8 (Karaya Gum-10mg) showed better and desired drug release pattern i.e.,97.09% in 12 hours.

Key Words: Frovatriptan, Prolonged Release Tablets, Migraine, Xanthan gum, Guar gum and Karaya gum.

INTRODUCTION:

The most preferred route for administration of dosage forms is oral route, due to its potential advantages like ease of administration, convenient dosing, self-medication, no pain and patient compliance. Hence tablets and capsules are the most popular dosage forms. With many drugs, the basic goal of therapy is to achieve a steady-state blood or tissue level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage regimens is an important element in accomplishing this goal. The idealized objective points to the two aspects most important to drug delivery namely, spatial placement and temporal delivery of a drug. Spatial placement relates to targeting a drug to a specific organ of tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An appropriately designed sustained release drug delivery system can be a major advance toward solving these two problems. The bulk of research has been directed at oral dosage forms that satisfy the temporal aspect of drug delivery, but many of the newer approaches under investigation may allow for spatial placement as well[1].

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. According to International Headache Society (IHS), acute migraine attack is a deliberating cerebrovascular disorder characterized by throbbing unilateral (though, in some cases, can be bilateral), pulsatile, and moderate to severe intensity pain which is often associated with incidences of nausea, vomiting, photophobia, and phonophobia. This pain is aggravated by physical activity of the patient. An untreated migraine attack can persist for 4 to 72 hours and significantly affect the quality of life of migraineur. In addition, migraine exhibits sexual dimorphism with a prevalence ratio of 7 : 3 among females and males, after the attainment of puberty. As per IHS, an ideal migraine therapy should focus on regaining the functional ability of patient as soon as possible in a cost-effective manner and therapeutic effect should last for longer duration. Such therapy will alleviate the patient fear to get migraine attack back and will help in improving their quality of life[2].

Triptans, 5-HT1B and 5-HT1D receptor agonists, are considered to be the first line therapy for treating the migraine attack. This therapeutic class comprises seven members, namely, sumatriptan, zolmitriptan, rizatriptan, eletriptan, almotriptan, naratriptan, and the latest one "frovatriptan." All triptans share similar pharmacodynamics but each of them comprises a different pharmacokinetic profile which makes each of them a unique of its kind. According to current clinical practice and IHS, triptans can be broadly classified into two main categories based on efficacy to achieve pain-free response after 2 hours of *per oral* administration of dosage form, namely, high

efficacy triptans comprising sumatriptan, zolmitriptan, rizatriptan, eletriptan, and almotriptan and low efficacy triptans comprising naratriptan and Frovatriptan[3].

In the present study, an attempt has been made to develop sustained release tablets of frovatriptan using different natural polymers. The concentration of polymers was chosen without significantly affecting the basic tablets characteristics. To ensure this, tablets were subjected to basic physical tests of tablets.

MATERIALS & METHODS:

Materials:

Frovatriptan was provided by Natco Labs, Hyderabad and Xanthan gum, Guar gum, Karaya gum, MCC pH 102, Magnesium stearate, Talc were obtained from SD Fine Chemicals Ltd, Mumbai.

Methodology[4, 5, 6]:

Analytical method development

a) Determination of absorption maxima

A solution containing the concentration 10 µg/ ml drug was prepared in pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400[51].

b) Preparation calibration curve

100mg of Frovatriptan pure drug was dissolved in 100ml of 6.8 pH phosphate buffer(stock solution)10ml of solution was taken and make up with100ml of 6.8 pH phosphate buffer(100µg/ml).from this 10ml was taken and make up with 100 ml of 6.8 pH phosphate buffer (10µg/ml). The above solution was subsequently diluted with 6.8 ph phosphate buffer to obtain series of dilutions Containing 0.3,0.6,0.9,1.2 and 1.5µg/ml of Frovatriptan per ml of solution. The absorbance of the above dilutions was measured at 244 nm by using UV-Spectrophotometer taking 6.8 pH phosphate buffer as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin

Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes[52].

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$ $\tan \theta$ = Angle of repose

h = Height of the cone , r = Radius of the cone base

Bulk density

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

$$\text{Bulk Density} = M / V_o$$

Where, M = weight of sample

V_o = apparent volume of powder

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100

drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula[53]:

$$Tap = M / V$$

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of inter particulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value[54].

For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

$$\text{Carr's Index} = [(tap - b) / tap] \times 100$$

Where, b = Bulk Density

Tap = Tapped Density

Formulation development of Tablets[7, 8]

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 7.3.The tablets were prepared as per the procedure given below and aim is to prolong the release of Frovatriptan. Total weight of the tablet was considered as 60mg.

Procedure

1) Frovatriptan and all other ingredients were individually passed through sieve no # 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Table 1: Formulation composition for tablets

Formulation Code	Frovatriptan	Xanthan gum	Guar gum	Karaya gum	Mag. Stearate	Talc	MCC pH 102
F1	2.5	5	-	-	3	3	QS
F2	2.5	10	-	-	3	3	QS
F3	2.5	15	-	-	3	3	QS
F4	2.5	-	5	-	3	3	QS
F5	2.5	-	10	-	3	3	QS
F6	2.5	-	15	-	3	3	QS
F7	2.5	-	-	5	3	3	QS
F8	2.5	-	-	10	3	3	QS
F9	2.5	-	-	15	3	3	QS

All the quantities were in mg

EVALUATION OF POST COMPRESSION PARAMETERS FOR PREPARED TABLETS

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula[9].

% Deviation = (Individual weight – Average weight / Average weight) × 100

Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation[10].

Thickness

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation[11].

Friability

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as[12]

% Friability = [(W1-W2) / W] × 100

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

Determination of drug content

Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Frovatriptan were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve[13, 14].

***In vitro* drug release studies**

Dissolution parameters

Apparatus	--	USP-II, Paddle Method
Dissolution Medium	--	6.8 ph phosphate buffer
RPM	--	50
Sampling intervals (hrs)	--	0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature	--	37°c $\pm$ 0.5°c

As the preparation was for drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile.

Procedure

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c $\pm$ 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated 6.8 ph phosphate buffer was removed and pH 6.8 phosphate buffer was added process was continued from upto 12 hrs at 50 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor

fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 244 nm using UV-spectrophotometer.[15, 16]

Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release[62]. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.[17, 18]

RESULTS:

The present study was aimed to developing Prolonged Release tablets of Frovatriptan using various Natural polymers. All the formulations were evaluated for physicochemical properties and invitro drug release studies.

Analytical Method

Graphs of Frovatriptan was taken in buccal pH that is in p H 6.8 phosphate buffer at 244 nm

Table 2: Observations for graph of Frovatriptan in pH 6.8 phosphate buffer (244 nm)

Concentration[µg/ml]	Absorbance
0	0
0.3	0.202
0.6	0.391
0.9	0.572
1.2	0.773
1.5	0.912

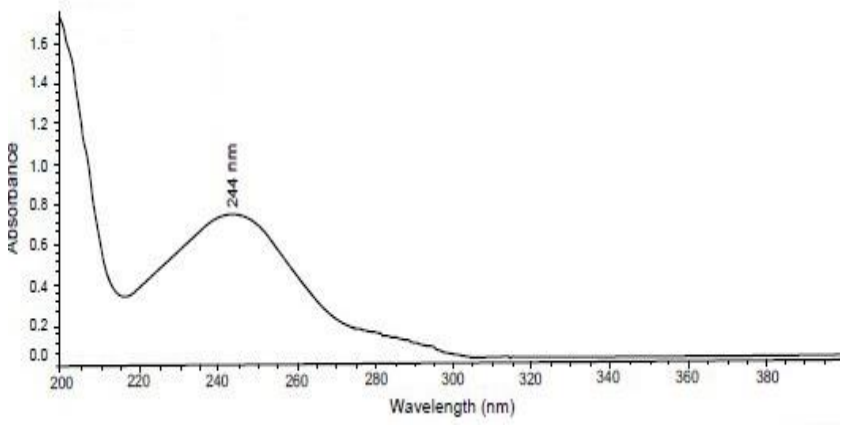

Fig 1: Absorption Maxima of Frovatriptan

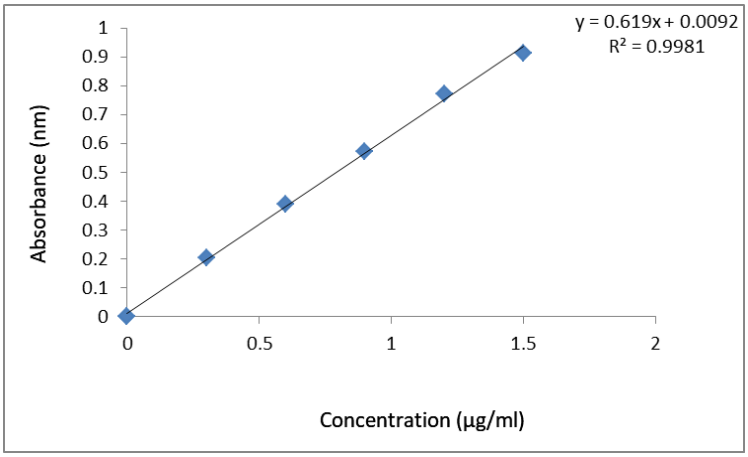

Fig 2: Standard graph of Frovatriptan in pH 6.8 phosphate buffer at λmax

Preformulation parameters of powder blend

Table 3: Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.98	0.54	0.56	15.03	0.98
F2	26.06	0.55	0.52	16.26	1.04
F3	23.35	0.53	0.53	14.24	1.15
F4	25.46	0.52	0.54	16.96	1.08
F5	26.03	0.55	0.55	15.95	1.23
F6	25.65	0.54	0.54	18.57	1.25
F7	24.98	0.52	0.56	19.26	0.99
F8	26.87	0.51	0.55	18.45	1.05
F9	25.19	0.55	0.54	16.98	1.08

Quality control Parameters for Tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness and drug release studies in different media were performed on the formulation of tablet.

Table 4: Post compression parameters

Formulation codes	Weight variation(mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	58	4.7	0.62	2.3	98.99
F2	60	4.1	0.54	2.6	96.49
F3	61	4.3	0.86	2.7	97.50
F4	59	4.7	0.58	2.8	98.28
F5	60	4.4	0.83	2.5	98.97
F6	62	4.3	0.58	2.6	96.14
F7	61	4.4	0.69	2.7	99.15

F8	63	4.3	0.56	2.8	97.29
F9	61	4.5	0.58	2.6	99.38

Invitro quality control parameters for tablets

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In-Vitro* Drug Release Studies**

Table 5: Dissolution Data of Frovatriptan Tablets Prepared with Xanthan gum In Different Concentrations

TIME (hr)	F1 (%)	F2 (%)	F3 (%)
0	0	0	0
0.5	6.11	8.97	8.07
1	9.57	14.58	13.56
2	16.85	23.43	18.95
3	24.97	28.96	26.78
4	32.57	39.04	41.81
5	41.70	45.95	47.27
6	49.38	53.96	57.36
7	58.90	60.47	66.05
8	63.76	69.05	71.57
9	70.94	78.34	77.05
10	78.10	82.20	82.27
11	84.57	86.05	86.56
12	90.05	92.59	92.25

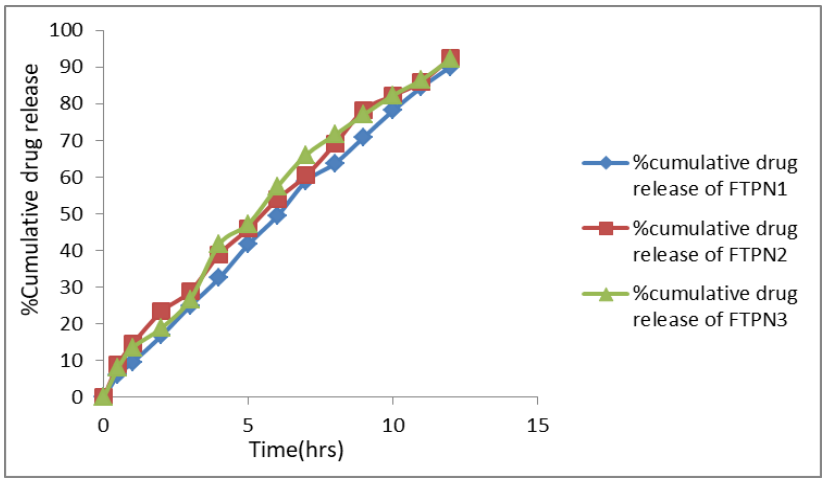

Fig 3: Dissolution profile of Frovatriptan (F1, F2, F3 formulations).

Table 6: Dissolution Data of Frovatriptan Tablets Prepared With Guar gum In Different Concentrations

TIME (Hr)	F4 (%)	F5 (%)	F6 (%)
0	0	0	0
0.5	7.06	7.04	8.06
1	13.48	11.06	10.41
2	19.97	16.93	15.39
3	25.06	25.04	22.21
4	29.34	34.50	28.48
5	40.95	41.17	39.96
6	47.96	49.96	50.04
7	52.19	57.04	56.81
8	60.97	67.25	65.96
9	68.37	71.05	73.07
10	74.09	78.96	78.85
11	80.99	84.16	85.07
12	88.04	89.35	92.16

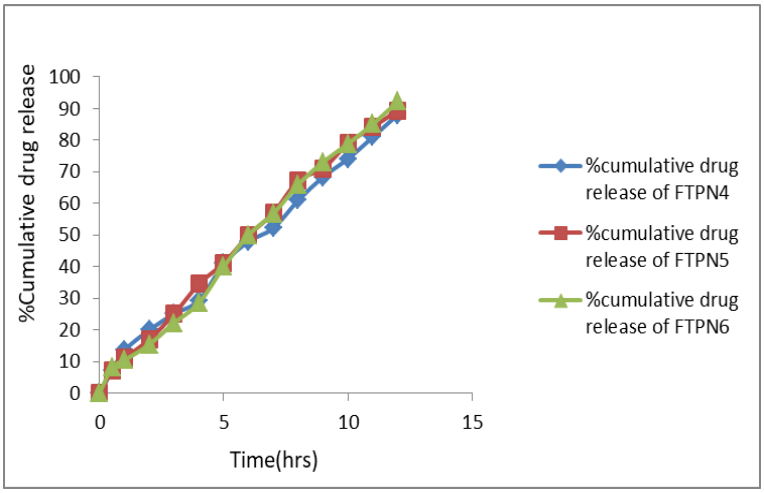

Fig 4: Dissolution profile of Frovatriptan (F4, F5, F6 formulations)

Table 7: Dissolution Data of Frovatriptan Tablets Prepared With Karaya gum In Different Concentrations

TIME (hr)	F7 (%)	F8 (%)	F9 (%)
0	0	0	0
0.5	7.05	7.05	8.14
1	13.17	12.16	12.83
2	16.38	19.29	17.26
3	23.04	27.26	22.09
4	29.16	38.98	27.21
5	37.95	47.24	38.04
6	48.29	55.87	46.81

7	55.27	62.30	52.05
8	62.06	71.07	59.96
9	70.81	78.60	64.14
10	77.35	84.06	72.94
11	82.37	92.88	78.16
12	89.95	97.09	82.95

Fig 5: Dissolution profile of Frovatriptan (F7, F8, F9 formulations)

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table 8: Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG (%) RELEASE	LOG (T)	LOG (%) REMAIN
		0			2.000
7.05	0.5	0.458	0.848	1.987	1.968
12.16	1	1.000	1.085	0.000	1.944
19.29	2	1.414	1.285	0.301	1.907
27.26	3	1.732	1.372	0.477	1.883
38.98	4	2.000	1.591	0.602	1.785
47.24	5	2.236	1.591	0.699	1.785
55.87	6	2.449	1.674	0.778	1.722
62.3	7	2.646	1.747	0.845	1.645
71.07	8	2.828	1.794	0.903	1.576
78.6	9	3.000	1.852	0.954	1.461
84.06	10	3.162	1.895	1.000	1.330
92.88	11	3.317	1.925	1.041	1.202
97.09	12	3.464	1.968	1.079	0.852

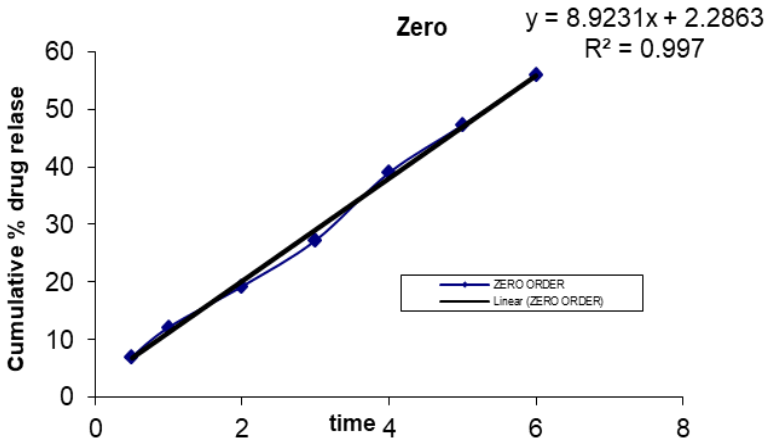

Fig 6: Zero order release kinetics graph

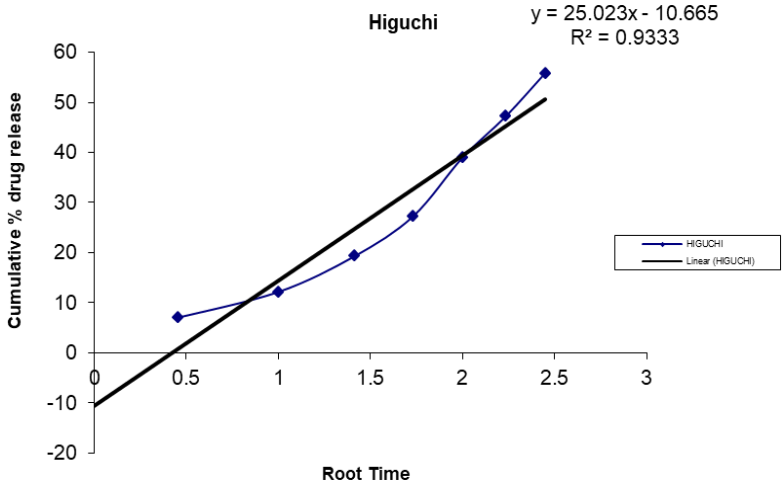

Fig 7: Higuchi release kinetics graph

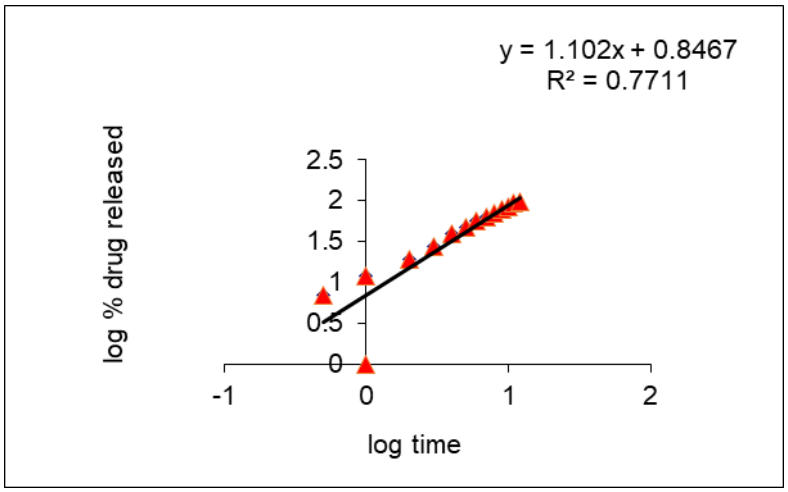

Fig 8: korsmeyer peppas graph

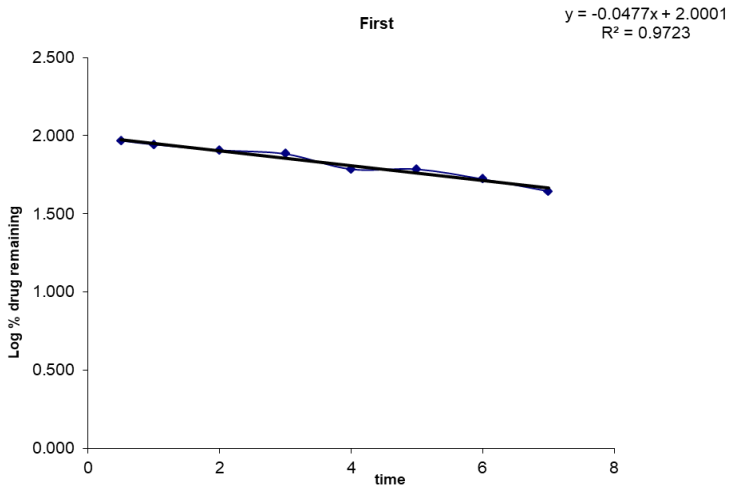

Fig 9: First order release kinetics graph

From the above graphs it was evident that the formulation F8 was followed Zero order release kinetics.

Drug and Excipient Compatibility Studies:

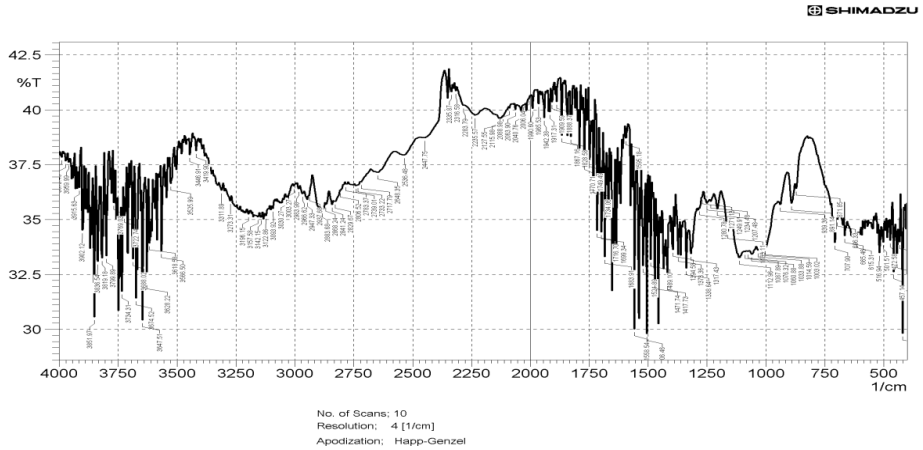

Fig 10: FTIR spectrum of pure drug

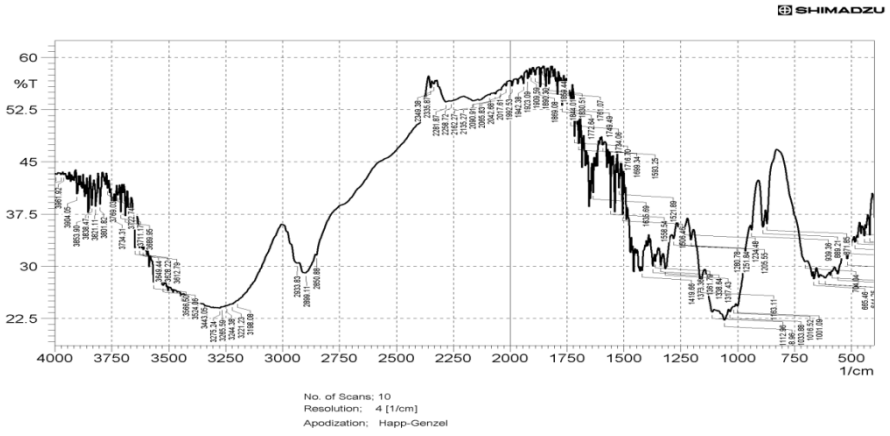

Fig 11: FTIR spectrum of optimized formulation

DISCUSSION:

The study was aimed to developing Prolonged Release Tablets of Frovatriptan using various Natural Polymers. All the formulations were evaluated for physicochemical properties and In-vitro drug release studies. Frovatriptan was taken in pH that is in pH 6.8 phosphate buffer at 244 nm in the table2. Standard graph of Frovatriptan in pH 6.8 phosphate buffer at λmax are in the given graph2. Pre-formulation parameters of powder blend formulation of F1 to F9 in the table3 and the tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the formulation of tablet of weight variation include of the post compression parameters of the table4. All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

In-vitro Drug release studies of the dissolution data of Frovatriptan tablets prepared with Xanthum gum in different concentrations. Dissolution profile of Frovatriptan the percentage cumulative drug release of F1, F2, F3 formulations in the table5 and figure3.

In-vitro Drug release studies of the dissolution data of Frovatriptan tablets prepared with Guar gum in different concentrations. Dissolution profile of Frovatriptan the percentage cumulative drug release of F4, F5, F6 formulations in the table6 and figure4.

In-vitro Drug release studies of the dissolution data of Frovatriptan tablets prepared with Karaya gum in different concentrations. Dissolution profile of Frovatriptan F7, F8, F9 formulations in the table7 and the figure5.

Various models were tested for explaining the kinetics of drug release. Release kinetics data for optimised formulation of table8. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order in figure6, Higuchi in figure7, Korsmeyer-Peppas release model in figure8 and first order release model in figure9.

CONCLUSION:

The aim of the present study was to develop Sustained Release Tablet formulation of Frovatriptan to maintain constant therapeutic levels of the drug for over 12 hrs. Xanthan gum, Guar gum and Karaya gum were employed as Natural polymers. Frovatriptan dose was fixed as 2.5 mg. Total weight of the tablet was considered as 60 mg. Polymers were used in the concentration of 5 mg, 10 mg and 15 mg concentration. Tablets were prepared by Direct Compression Technique. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation F8 (Karaya Gum-10mg) showed better and desired drug release pattern i.e., 97.09% in 12 hours.

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CONFLICT OF INTEREST:

The authors don't have any conflict of interest.

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