STABILITY STUDY OF POST-SHELF LIFE AND MARKETED TABLETS OF FROVATRIPTAN BY RP-HPLC

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ABSTRACT

The stability of pharmaceutical products plays an important role from the economic point of view. There are not many studies that report about the stability of drugs past their expiration dates. The objective of the current study was to determine the tablet content of expired tablets of Frovatriptan where expiry date has not exceeded and to develop simple, accurate, sensitive and stability indicating RP-HPLC method for the determination of per cent drug remained of Frovatriptan in the presence of its degradation products in bulk drug, expired tablets and tablets whose expiry date has not been exceeded. Drug was subjected to all stress conditions such as hydrolysis (acidic and alkaline), oxidation, photolysis, thermal degradation and humidity study. Content determination was performed using RP-HPLC method; the percent of dissolved substance from tablets was also performed. All stressed samples were successfully analyzed on C_{18} column using mobile phase acetonitrile: methanol: 0.1% orthophosphoric acid 45:15:40 (v/v/v) mobile phase (p^H5.6). A flow rate was maintained at 1 Ml/min and detection was made at 245 nm. The proposed method was validated with regard to linearity, sensitivity and accuracy and precision. No discrepancies between the results of determination and the declared values range for all the analyzed tablets were observed. The results of performed study might suggest that storage of analyzed batches of tablets over time period exceeding the expiry date given by the manufacturer did not influence their contents.

Keywords: *Frovatriptan, Stability, Expired Tablets, RP-HPLC.*

INTRODUCTION

In recent years, growing interest in drug stability problem has been observed. The application of modern technologies and new substances during drug formulation processes as well as high quality of tablet containers and meeting GMP and GLP requirements may result in improvement of drug stability and inaccurate expiry date ranges declared by the manufacturers. Another point is a requirement of harmonization of analytical procedures and method validation for laboratories performing stability testing of existing drug substances. If analysis of tablet stability is considered, the most important ones are content determination. Generally the expired drug is characterized by more than 10% of product degradation and any changes of physicochemical properties e.g. color, odour, taste or appearance. The changes in dissolution profile also might be the result of ageing of the product[1].Though the drug expiration dates are meant to indicate the date at which the drug potency begins to diminish, the expiration date does not indicate that a drug will be ineffective or harmful after the date listed on the box or bottle, or the said drug may still be good on the manufacturer's chosen date; and the expiration date has little to do with scientific testing because most medications are probably potent and even safe after expiration date and the FDA has little control over the chosen dates[2].

The objective of the present study was to determine tablet content and perform dissolution test of expired tablets of Frovatriptan and tablets whose expiry date has not exceeded of and to determine per cent drug remained of Frovatriptan in the presence of its degradation product in bulk drug, expired tablets and tablets whose expiry date has not been exceeded. The analyzed tablets contained 2.5 mg of Frovatriptan. The drug Frovatriptan[3-5] (FVT brand name Frova) 5-HT receptor agonist that binds with high affinity to 5-HT$_{1B}$ and 5- HT$_{1D}$ receptors. It has no significant effects on GABA mediated channel activity and has no significant affinity for benzodiazepine binding sites. Frovatriptan is believed to inhibit excessive dilation of extra cerebral intracranial arteries in migraine. It is used for the acute treatment of migraines with or without aura in adults. Its efficacy, long duration of action and good tolerability profiles show considerable potential in acute and prophylactic management of menstrual migraines.

The aim of the study was to clarify the problem of drug stability over the expiry period declared by the producer. Thus the drug chosen (Frovatriptan) was not the newly synthesized substance but, the one with good established position in the pharmaceutical product. Stress testing of the drug substance can help identify likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedure used[6].

By keeping all this in view, it was thought

worthwhile to perform comparative correlation of the developed method for stability indication of Frovatriptan in laboratory sample, marketed and expiry formulation. Literature survey revealed that many visible[7-10] and other analytical methods[11-12] are available for estimation of Frovatriptan but comparative quality evaluation of expired and marketed Fraovatriptan tablets are not yet reported.

EXPERIMENTAL

Chemicals Standard Frovatriptan was gifted by Sun Pharma, Ahmedabad. Ltd as a gift sample whereas the branded formulation of Zomig was procured from the local market (mfg.date FEB, 2014 and exp. date FEB,2017). All the chemicals and reagents used were of analytical grade and were procured from LOBA Chemie Pvt. Ltd. (Mumbai, India).

INSTRUMENTATION

Analysis of all samples were performed using a Shimadzu VP series HPLC model chromatograph equipped with a reverse phase Phenomenex Chromosil C-18 column (250mm×4.6 mm, 5μ). The chromatographic separation is carried out in isocratic mode Inertsil C_{18} (250 mm, 4.6 mm, 5μ) column as stationary phase with the volume of an injection loop (Rhedyne 7725) of 20μl. The data was processed by using total chrome navigator software. All samples were filtered through 0.45 micrometer membrane Millipore filtration apparatus with vaccum pump. The dissolution test was performed using Dissolution test system (Model No.DA-3) of Veego Scientific devices.

Chromatographic Conditions

Stability indicating HPLC assay method was developed on a Shimadzu VP series HPLC model chromatograph equipped with a reverse phase Phenomenex Chromosil C-18 column (250mm×4.6 mm, 5μ). The chromatographic separation is carried out in isocratic mode Inertsil C_{18} (250 mm, 4.6 mm, 5μ) column as stationary phase with the volume of an injection loop (Rhedyne 7725) of 20μl. The mobile phase consisted of acetonitrile, methanol and ortho phosphoric acid in the ratio of 45:15:40(v/v/v) at a flow rate of 1.0ml/min. The p^H of the mobile phase was adjusted to 5.6 by adding 0.1% orthophosphoric acid drop by drop. The detection of wavelength was set at 245 nm with a run time of 10min. The analytical wavelength was set at 245 nm. Intially the method was developed for standard Frovatriptan and then it was performed on laboratory samples, marketed tablet and expired tablet of Frovatriptan for per cent estimation and then it was extended to stress samples. The standard to all stress samples were prepared in methanol.

Preparation of Mobile Phase

The mobile phase was prepared by mixing acetonitrile, methanol and ortho phosphoric acid in the ratio of 45:15:40 (v/v/v) at a flow rate of 1.0ml/min. The solution was filtered, sonicated for 20 minutes for degassing and used as mobile phase. The p^H of the mobile phase was adjusted to 5.6 by adding 0.1% orthophosphoric acid drop by drop and the flow rate of the mobile phase was maintained at 1.0ml/min.

Preparation of Frovatriptan Standard Solution

An accurately weighed amount of tablet powder equivalent to 100mg was dissolved in 100 ml of methanol and the solution was finally made up with the same. The concentration of the resulting solution was found to be 1 mg / ml. From the stock solution suitable dilutions were made to obtain final working concentrations of 50μg/ml.

Sample Preparation (for Marketed and Expired Formulation of Frovatriptan)

Synthetic mixture powder or formulation powder equivalent to 100 mg of drug was accurately weighed and transferred to a 100 ml volumetric flask. 40 ml of mobile phase was added and sonicated for 10 min. The volumes were made upto the mark with mobile phase and filtered through a 0.45μ nylon membrane filter. From the stock solution suitable dilutions were made to obtain the working standard concentrations of 50 μg/ml.

Forced Degradation Studies (Stress Testing)

Frovatriptan is a selective 5-$HT_{1B/1D}$ − receptor agonist that has chemical structure susceptible to degradation and therefore in this work forced studies of drugs were carried out by a validated stability indicating liquid chromatographic method developed. Stress testing was performed on drug substance under hydrolysis (0.1N HCl, 0.1 N NaOH and water), oxidation (3% H_2O_2), heat (70⁰C) and photolysis (UV and VIS radiation) as mentioned in ICH QIA (R2).

Stress testing was carried out according to the ICH stability testing guidance and drug was stressed under various conditions in order to facilitate 5-30% degradation. For each specific condition maintained, a blank solution was prepared and was subjected to stress in the same manner as the drug. A control solution of drug was prepared, which was stored without the stress condition and the results of degradation studies are presented in the Table 3.

Hydrolysis is one of the most common degradation chemical reactions over wide range of pH. Hydrolysis is a solvolytic process in which drug reacts with water to yield break down products of different chemical compositions. Water either as a solvent or as moisture in the air comes in contact

with pharmaceutical dosage forms is responsible for degradation of most of the drugs. The hydrolytic degradation of a new drug in acidic and alkaline conditions can be studied by refluxing the drug in 0.1N HCl/ 0.1N NaOH for 8 hrs. If reasonable degradation is seen, testing can be stopped at this point. However, in case no degradation is seen under these conditions, the drug should be refluxed in acid/alkali of higher strengths and for longer duration. Alternatively, if total degradation is seen after subjecting the drug to initial conditions, acid/alkali strength can be decreased along with decrease in the reaction temperature. In a similar manner, degradation under neutral conditions can be started by refluxing the drug in water for 12 hrs. Reflux time should be increased if no degradation is seen. If the drug is found to degrade completely, both time and temperature of study can be decreased.

Forced degradation studies are designed to test the susceptibility of compounds to oxidative degradation. Many drug substances undergo autoxidation i.e., oxidation under normal storage condition and involving ground state elemental oxygen. Therefore it is an important degradation pathway of many drugs. Autoxidation is a free radical reaction that requires free radical initiator to begin the chain reaction. Hydrogen peroxide, metal ions, or trace level of impurities in a drug substance act as initiators for autoxidation. Hydrogen peroxide is very common oxidant to produce oxidative degradation. It can be used in the concentration range of 3-30% at a temperature not exceeding 40°C for 2-8 days. The oxidative stress testing is initially carried out in 3% H_2O_2 at room temperature for 6 hrs and it can be increased/ decreased to achieve sufficient degradation. The time can also be increased up to 24 hrs with 30% or decreased upto 30 min with 1% of H_2O_2.

Photolytic degradation is carried out by exposing the drug substance (in solid as well as in the solution form) or drug product to a combination of UV and Visible light. The most commonly accepted wavelength of light is in the range of 300-800 nm to cause the photolytic degradation. The photolytic degradation can occur through non oxidative or oxidative photolytic reaction. The no oxidative photolytic reaction include isomerization, dimerization, cyclization, rearrangements, decarboxylation and hemolyticcleavage of X-C-hetero bonds, N-alkyl bond (dealkylation and deamination), SO_2-C bonds etc and while oxidative photolytic reaction occurs through either singlet oxygen ($^1O_2$) or triplet oxygen ($^3O_2$) mechanism. The singlet oxygen reacts with the unsaturated bonds, such as alkenes, dienes, polynuclear aromatic hydrocarbon to form photoxidative degradation products, whereas triplet oxygen reacts with free radical of the drug molecule, which then form peroxide. Hence, light can also act as a catalyst to oxidation reactions. The overall illumination showed not to be less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200 W-h/m. However, illumination is decreased or increased to achieve sufficient degradation. The maximum illumination recommended is 6 million lux hrs.

Forced degradation studies designed to test the stability of compounds by exposing them to different thermal and humidity conditions. In general, rate of a reaction increases with increase in temperature. Hence, the drugs are susceptible to degradation at higher temperature. Many APIs are sensitive to heat or tropical temperatures, for example, vitamins, peptides, etc. Thermal degradation involves different reactions like pyrolysis, hydrolysis, decarboxylation, isomerisation, rearrangement and polymerization. Effect of temperature on thermal degradation of a substance is studied through Arrhenius equation:

$$K = Ae^{-Ea/RT}$$

Where K is specific reaction rate, A is frequency factor; Ea is energy of activation, R is gas constant (2 cal/deg mole) and T is absolute temperature.

Thermal degradation study is carried out at 40°C to 80°C. The most widely accepted temperature is 70°C at low and high humidity for 1-2 months. High temperature (>80°C) may not produce predictive degradation pathway. The use of high-temperatures in predictive degradation studies assumes that the drug molecule will follow the same pathway of decomposition at all temperatures. This assumption may not hold true for all drug molecules and therefore great care must be taken in using the extreme temperatures easily accessible in a sealed-vessel microwave experiment for predictive degradation studies.

Dissolution Test

In the next step, release profiles of marketed and expired tablets of Frovatriptan were examined using dissolution test apparatus, performed using multi bath (n=6) apparatus with paddles. A dissolution medium was 0.01M HCl, the paddle speed was 75 rpm and the medium volume was 900 mL. The medium was maintained at 37°C. The glass dissolution vessels were covered to minimize evapouration. The samples of marketed and expired tablets of Frovatriptan were taken at appropriate intervals at 5,15,25,35 and 45 min and assayed spectrophotometrically at 245 nm.

Method Validation

Validation of developed analytical method was performed as per ICH guidelines Q2B[8], over the linearity, accuracy, precision, specificity, limit of detection, limit of quantization and robustness.

RESULTS AND DISCUSSION
Selection of Wavelength and Chromatographic Condition for RP-HPLC Method

Optimization of mobile phase was performed based on sharp and well resolved peak of drug obtained, asymmetric factor and theoretical plates obtained of Frovatriptan. Mixture consisting of acetonitrile, methanol and 0.1% ortho phosphoric acid were examined at different proportions like 75:20:5 (v/v/v) 70:25:5 (v/v/v) 69:12:20 (v/v/v) 80:18:2 (v/v/v) and 71:25:4 (v/v/v). A mixture of acetonitrile, methanol and 0.1% Ortho phosphoric acid in the ratio 45:15:40 (v/v/v) was selected which gave sharp, well resolved peak of Formitriptan. The retention time of drug was 3.0 min. UV spectrums showed that the drug was absorbed appreciably at 245 nm, so the wavelength was selected as the detection wavelength during studies. The calibration curve was found to be linear over the range of 20-100 mcg/mL. The developed method was extended to laboratory sample, marketed and expired formulation.

Validation of method

The accuracy of the method was determined by calculating recoveries of Frovatriptan marketed and expired tablets at concentration level 80%, 100% and 120% by method of standard addition. The recoveries obtained were 99.99 and 99.25% respectively. The high values indicate that the method is accurate. Instrument precision was determined by performing repeatability test and the RSD values for bulk drug, marketed and expired Frovatriptan were found to be 0.99, 0.29 and 0.9985 respectively. This is within limit i.e. less than 1 for bulk drug and less than 2 for finished products. The inter, intra-day and different analytical studies were performed and mean of concentration did not deviate from the nominal concentration. The inter, intra-day and different analytical precision studies were carried out and the RSD values for marketed formulations was found to be 0.00193, 0.00176 and 0.00267 respectively. The low RSD values indicate that the method is precise. The detection limit for Frovatriptan was 0.0299 while quantization limits was 0.099.

Analysis of stressed samples

The ICH stability guideline Q1A (R2) defines stress testing for new drug substances and drug products, to elucidate the intrinsic stability of the drug substances and drug products. The stress testing may also provide information about degradation pathways and selectivity of the applied analytical method.

Stress testing was performed on drug substance under hydrolysis (0.1N HCl, 0.1N NaOH and water), oxidation (3% H_2O_2), heat (70°C) and photolysis (UV and VIS radiation) as mentioned in ICH QIA (R2). % in acidic condition (Fig.2.3) and in alkali degradation, it was found that around 39.64 % of the drug degraded (Fig.4). In hydrolytic condition, it was found that around 45.19 % of the drug degraded (Fig.5), 42.29% and 40.15 % of the drug degraded in oxidative Fig.2.6) and thermal degradation condition (Fig.7). A major degradation (15-42%) is observed in photolytic condition. Retention time of major degradation product is at 33.9 & 45.19 minutes, respectively.

The developed method was extended to marketed and expired tablets of Frovatriptan and it was observed that there is almost similar degradation pattern found in case of both and they are less prone to force degradation studies as compared to bulk drug, only exception found in case of humidity study.

There is no considerable change found in % drug remained under various conditions of stress studies performed on expired formulation with marketed formulation. This shows that even after 1 year expiry Frovatriptan tablet, it is effective and potent too as its per cent estimation under normal conditions is 99% by RP-HPLC method which is within the limits i.e.90-110 % for Frovatriptan tablets as per official standards.

Table 1: Optimized chromatographic conditions for estimation of FVT

S. No	Parameters	Values
1	Elution	Isocratic
2	A.P.I Concentration(μg/ml)	10
3	Mobile Phase/Diluent	Acetonitrile:methanol:0.1% orthophosphoric acid 45:15: 40 (v/v/v)
4	pH	5.6
5	Column	C_{18}, (250mm×4.6 mm, 5μ)
6	Wave Length(nm)	245
7	Flow rate(ml/min)	1.0
8	Column temperature	Ambient
9	Volume injection(μl)	20

Table 2: System suitability parameters and Precision of the proposed method for FVT

S.No	Parameter	FVT (M_2)
1	Retention time (t), (min)	3.068
2	Theoretical Plates (n)	8284
3	Peak area	837046.2
4	Linearity(µg/ml)	20 -100
5	Regression equation (y = mx + C)	
	Slope (m)	1992x
	Intercept (b)	1219.8
6	Standard deviation on slope (Sm)	30.05
7	Standard deviation on intercept (Sb)	1995.04
8	Standard error of estimate (Se)	1902.2
9	Correlation coefficient (r)	0.9996
10	Limit of Quantification(µg/ml)	0.0997
11	Limit of Detection(µg/ml)	0.0299
12	% of RSD [*]	0.9993
13	Percent range of errors (confidence limits)	
	0.05 level	±0.2992
	0.01 level	±0.9976
14	Pump pressure (psi)	8-9
15	Tailing factor	1.68

* Mean of five determination

Table 3: Assay and Recovery of FVT (expired) in dosage forms

Method	Pharmaceutical formulation	Labelled amount (mg)±S.D	Proposed method			Amount found by reference method±S.D	% Recovery by proposed methods±S.D [**]
			Amount found [*]	t (valu e)	F (value)		
M_2	Frova	2.5±0.043	2.503	0.84	2.58	2.38±0.031	95.2±0.84
		5±0.032	5.978	1.45	1.49	5.267±0.097	101.2±0.47

Dissolution Studies

Release profiles were examined using dissolution tests for both marketed and expired tablets of Frovatriptan. The % cumulative drug releases of marketed and expired Frovatriptan tablets were found to be 77.97% and 72.13% within 45 min. This shows that expired and not expired tablets means marketed tablets were found to be almost similar rate of release profile in 0.01 M Hcl and which is within the limit i.e. 70 % release in 45 min as per IP[19].

Table 4: Linearity results

S. No	Concentrations (µg/ml)	Area of the peak
1	20	41003 ± 3.654
2	40	81120 ± 3.322
3	60	119227±3.985
4	80	163151± 4.890
5	100	199182±5.364

Table 5: Stability of the standard solution

Time	FVT	
	% Assay	% Difference
Initial	99.13	---
12th hr	98.80	0.33
18th hr	98.82	0.31
24th hr	98.63	0.53

Table 6: Intraday Precision

S. No.	Concentration (ug/ml)	Inter day Precision Mean n=3	% Amt. calculated	% RSD
1	15	15.08	100.53	0.970
2	30	30.12	100.40	0.955
3	45	45.25	100.55	0.822

Table 7: Inter day precision

S. No.	Concentration (µg/ml)	Intra-day Precision mean n=3	% Amt. Calculated	% RSD
1	15	14.78	98.53	0.961
2	30	29.96	99.88	0.817
3	45	44.90	99.77	0.752

Table 8: Accuracy data of the proposed method

Amount of the standard drug added	Amount of the standard drug found (µg/ml)	% recovery	% mean recovery	% RSD
30	30.14	100.47	100.47	1.12
30	30.53	101.76		
30	29.76	99.20		
50	49.56	99.12	100.07	0.97
50	50.49	100.98		
50	49.84	100.11		
70	69.25	99.6	100.19	1.11
70	70.22	100.31		
70	70.47	100.67		

Table 9: Robustness evolution of RP-HPLC

S. No	Variation	Chromatographic parameters	
		Tailing factor	Theoretical plates
1	20% of methanol in the mobile phase	1.68	8284
2	10% of methanol in the mobile phase	1.88	7837
3	Flow rate at 0.9ml/min	1.0	8451
4	Flow rate at 1.1ml /min	1.37	6543
5	P^H of the mobile phase 5.4	1.47	4719
6	P^H of the mobile phase 5.8	1.65	5538

Table 10: Specificity study

Name of the Solution	Retention time in minutes
Blank	No. Peaks
Standard	1.9
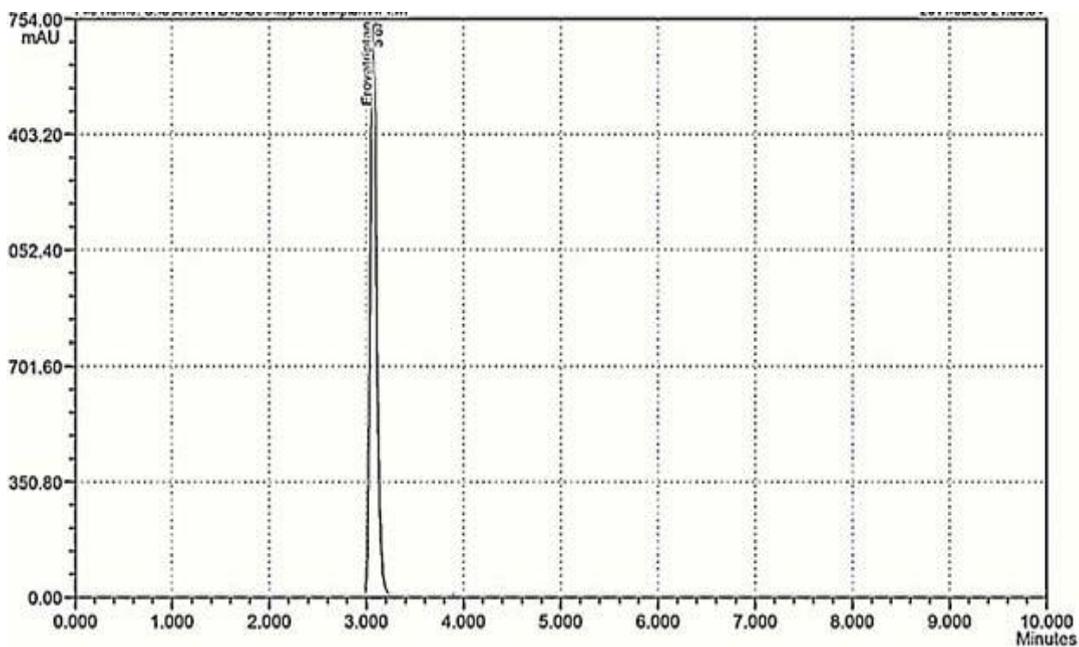
Fig. 1: Typical chromatogram of FVT standard
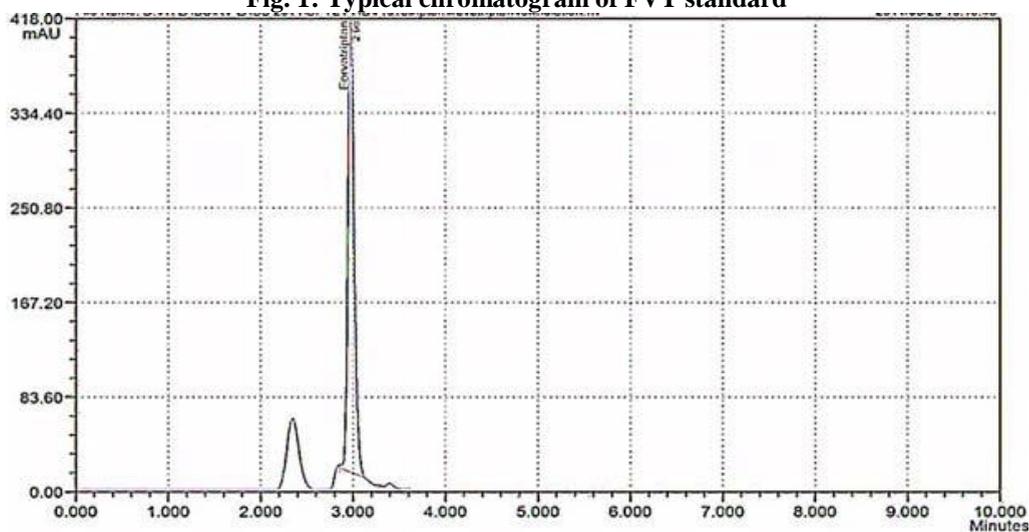
Fig. 2: Typical chromatogram of FVT formulation

Table 11: Forced degradation study results of FVT

Stress conditions	Degradation studies (Hrs.)	FVT	
		% Assay	% Degradation
Control		99.9	-----
Acid hydrolysis	8	60.48	39.46
Base hydrolysis	8	60.26	39.64
Hydrolytic	8	54.71	45.19
Oxidative	6	57.61	42.29
Thermal	48	59.75	40.15
Photolytic degradation (VIS)	48	66	33.9
Photolytic degradation(UV)	48	54.71	45.19

The Figs 3 to 9 show chromatograms of stressed samples and internal standard, which prove the stability-indicating capability of the assay.
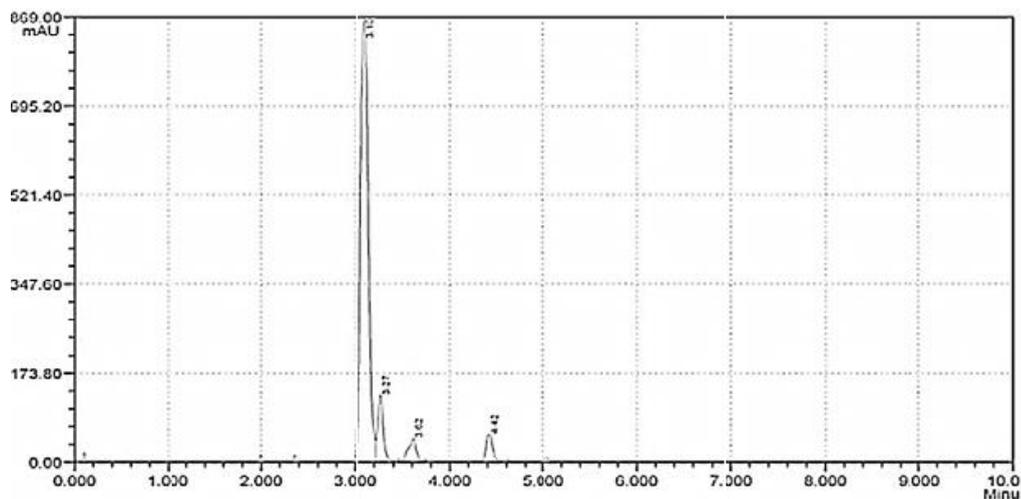
Fig. 3: Chromatogram of acid degradation of FVT
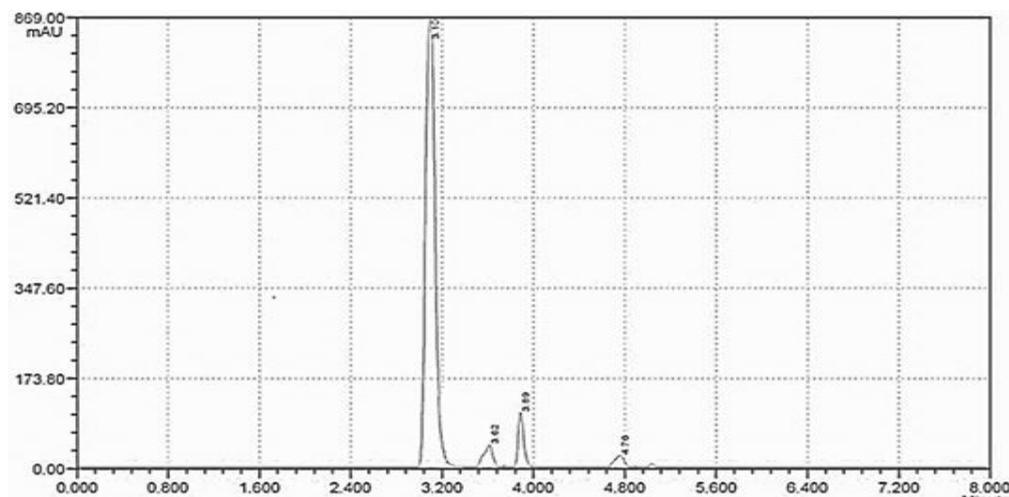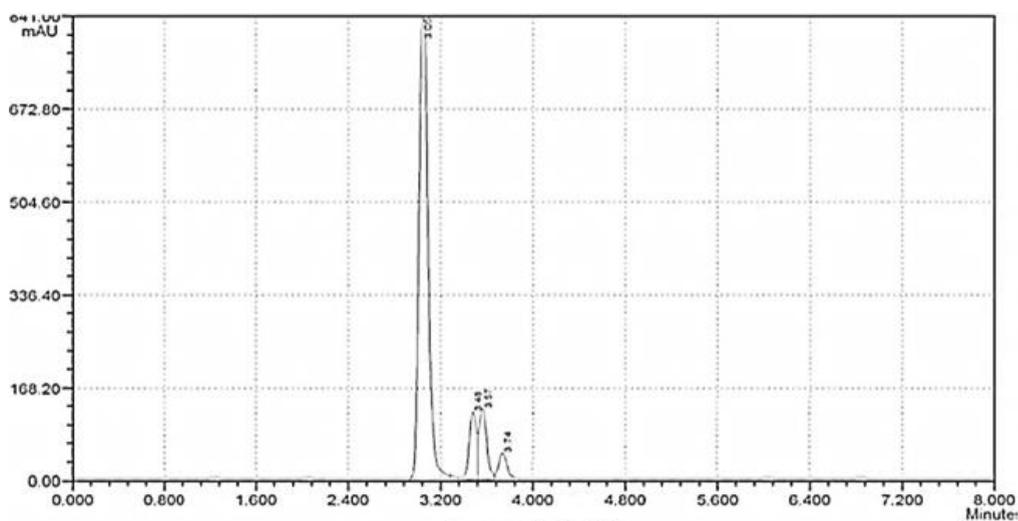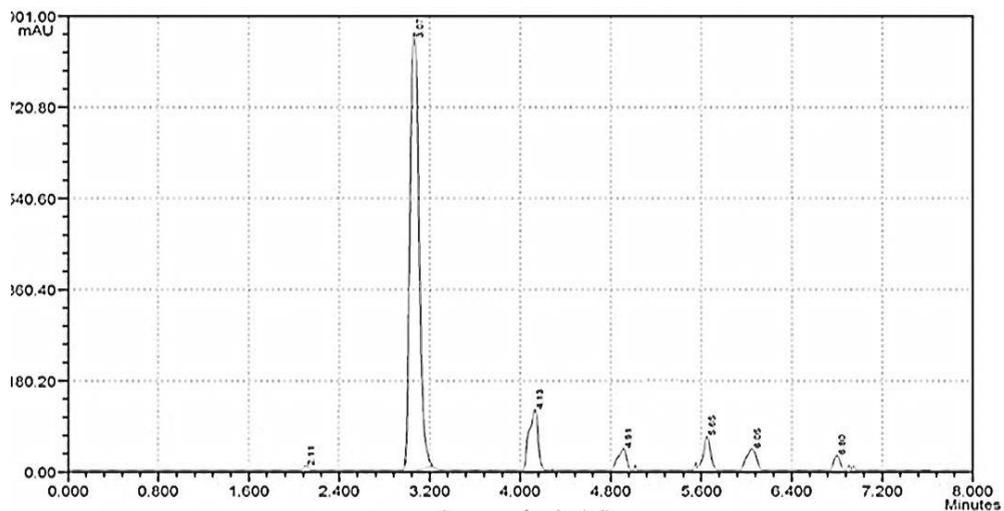

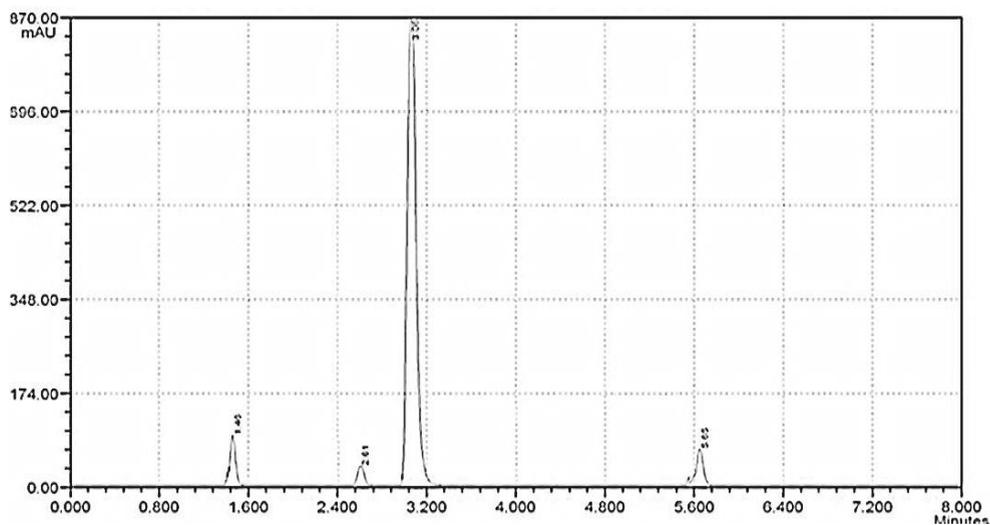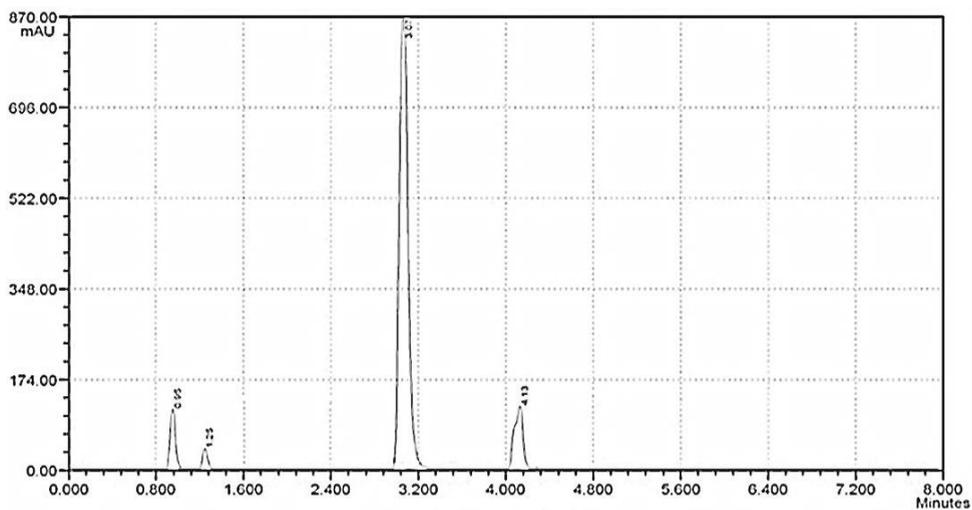**Fig.4: Chromatogram of base degradation of FVT**

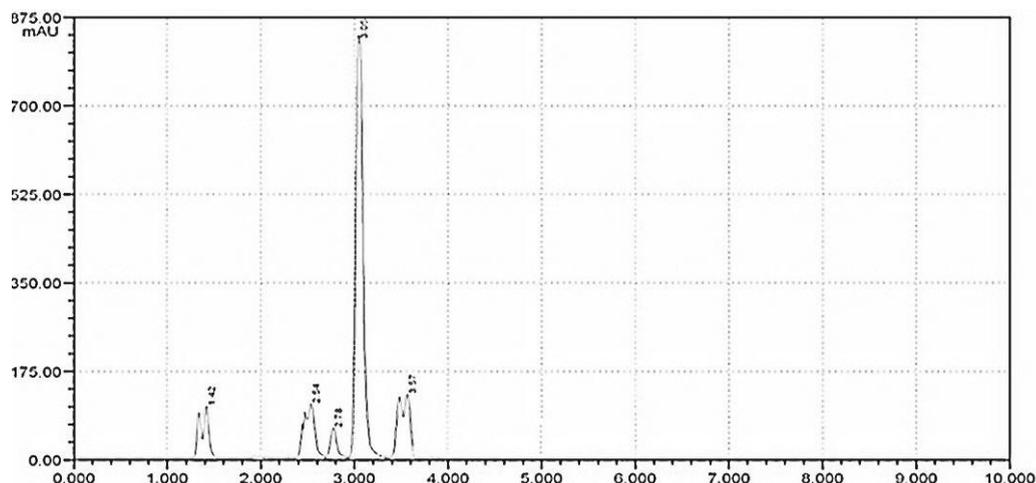**Fig. 5: Chromatogram of hydrolytic degradation of FVT**

Fig.6: Chromatogram of oxidative degradation of FVT

Fig.7: Chromatogram of thermal degradation of FVT

Fig.8: Chromatogram of Photo stability (VIS) degradation of FVT

Fig.9: Chromatogram of Photo stability (UV) degradation of FVT

CONCLUSION

The proposed RP-HPLC method for the estimation of the tablet content is characterized by good linearity, sensitivity as well as accuracy and precision. This study reflects the development of selective and validated stability indicating RP-HPLC method for Frovatriptan which could separate the drug and its degradation products formed under a variety of stress conditions under various ICH recommended guidelines. Based on the RP-HPLC studies it can be concluded that Frovatriptan was found to be more unstable in the solution state as compared to the solid state. It can also be concluded that the drug undergoes more degradation in hydrolysis study especially acid hydrolysis and oxidative stress studies. Bulk drug is also found to be prone to direct UV light. Only in case of humidity study bulk drug was more stable than its formulation. Based on almost similar result of release rate, per cent estimation and per cent drug remained under stress studies of marketed and 1 year expiry tablet of Frovatriptan it can be concluded that if drug stored under reasonable conditions it can retain 90% of their potency for at least few years after the expiry date on the label and sometimes much longer. The results of this study including both tablet content analysis and estimation of dissolution profiles might suggest that the storage of analyzed batches of tablets containing Frovatriptan over time period exceeding the expiry date given by the manufacturer did not influence their contents. The proposed RP-HPLC method proved to be effective for the determination of Frovatriptan during stability testing of both the bulk drug as well as pharmaceutical dosage form.

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