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A NOVEL UV SPECTROPHOTOMETRIC METHOD FOR THE DETERMINATION OF GILTERITINIB FUMARATE IN BULK AND PHARMACEUTICAL DOSAGE FORM - ANTINEOPLASTIC DRUG

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ABSTRACT

Objective: Gilteritinib fumarate is a tyrosine kinase inhibitor with potential antineoplastic activity. The aim of the present study was to develop and validate a simple, economic, precise and accurate UV spectrophotometric method for the quantification of Gilteritinib fumarate in bulk and tablet dosage form. **Methods:** The absorption maximum of the drug was observed at 230 nm using acetonitrile and water in the ratio of 50:50 as a solvent. The developed method was validated for specificity, accuracy, precision, linearity, LOD, LOQ and robustness as per ICH Q2 R1 guidelines. **Results and Discussion:** In accuracy studies the percentage recovery of the drug was found to be 99.28 %. The relative standard deviation values during precision studies were found to be less than 2%. Linearity was obtained in the concentration range of 5-35 µg/ml and correlation coefficient (r2) was found to be 0.999. The LOD and LOQ values of the developed method were found to be 0.115 µg/ml and 0.349 µg/ml respectively. **Conclusion:** Hence a simple and economic UV spectrophotometric method was developed for the estimation of Gilteritinib fumarate in bulk and pharmaceutical dosage form.

INTRODUCTION

A targeted therapy during cancer treatment uses drugs to target specific genes and proteins that are involved in the growth and survival of cancer cells. This therapy identifies and attacks cancer cells while causing less damage to normal cells. Tyrosine kinase inhibitors are a class of chemotherapy medications that inhibit the enzyme tyrosine kinases used in targeted therapy. Gilteritinib fumarate is the fumarate salt form of Gilteritinib, an inhibitor of the receptor tyrosine kinases with potential antineoplastic activity. It is chemically (E)-but-2-enedioic acid;6-ethyl-3-[3-methoxy-4-[4-(4-methylpiperazin-1 yl)piperidin-1-yl]anilino]-5-(oxan-4-ylamino) pyrazine-2-carboxamide. It is approved to treat acute myeloid leukemia. Extensive literature survey revealed there is an RP-HPLC method reported for the estimation of Gilteritinib in bulk and pharmaceutical dosage form [1]. There are few bioanalytical liquid chromatographic methods proposed for the estimation of tyrosine kinase inhibitors [2-4]. From the literature review it was found that there is no UV spectrophotometric method yet proposed for the estimation of Gilteritinib fumarate. Hence in the present study a simple and economic UV spectrophotometric method

was developed and validated according to ICH Q2 R1 guidelines [5].

MATERIALS AND METHODS

Gilteritinib fumarate pure drug and the tablet formulation containing 40 mg of Gilteritinib was procured from Spectrum Pharma Research Solutions (Hyderabad). Acetonitrile and HPLC grade water of analytical grade from Merck (Mumbai).

Instrumentation:

The analytical instrument used in the study was Shimadzu double beam UV-VIS spectrophotometer (UV-1800) which possesses a double beam double detector configuration with 1 cm quartz cells.

Selection of solvent:

The acetonitrile and water in the ratio 50:50 v/v was optimized as the solvent.

Standard solution preparation:

Accurately 20 mg of pure drug was weighed and dissolved in 10 ml volumetric flask and volume was made up to the mark with solvent. This was labeled as primary standard stock solution. From this solution, 1ml was taken into 10 ml volumetric flask and volume was made up to the mark with diluent. This was labeled as secondary stock solution. The working standard solution was prepared by pipetting 1 ml of secondary stock in to 10 ml volumetric flask and the volume was made up to the mark with solvent so as to get a final concentration of 20 µg/ml.

Sample solution preparation:

From the blend of 20 tablets, weight of powder equivalent to 20 mg of drug has taken into 10 ml volumetric flask, 5 ml of solvent was added and sonicated for 20 min. The resultant solution was filtered and volume was made up to 10 ml with diluent. This was labeled as primary sample stock solution. From this, 1 ml was taken into 10 ml volumetric flask and volume was made up to the mark with diluent. This was labeled as secondary sample stock solution. The working sample solution was prepared by pipetting 1 ml secondary sample stock in to 10 ml volumetric flask and the volume was made up to the mark with diluent.

Method Development:

Solubility check of the drug in various solvents has been carried out in various solvents such as water, methanol, chloroform, acetonitrile, 0.1 N hydrochloric acid, 0.1 N sodium hydroxide. From the above solvents, acetonitrile and water in the ratio of 50:50 was chosen as solvent for UV spectrophotometric analysis as it gave distinct spectrum with Gaussian distribution and good absorbance. The λmax of Gilteritinib fumarate in acetonitrile and water in the ratio of 50:50 %v/v as diluent was found at 230 nm. The UV spectrum was shown in Fig. 1.

RESULTS AND DISCUSSION

Method Validation:

The developed UV spectrophotometric method was validated for parameters like specificity, linearity, accuracy, precision, LOD, LOQ and robustness according to ICH guidelines [5].

Specificity:

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. To determine specificity of the method, blank and sample solutions were made and the spectra were noted then compared with spectrum of the analyte. No interference of either solvent or excipients was observed.

Precision:

Precision of method was verified by repeatability and intermediate precision. Repeatability was checked by assessing six individual homogenous preparations of standard solution under the same operating conditions over a short interval of time. Relative standard deviation (RSD) was calculated for absorbance of six determinations at the working concentration level of 20 µg /ml. The results are reported in table 1. Intermediate precision studies were done in two days by two different analysts. The results are reported in table 2. The RSD values were found to be less than 2 and hence assure the precision of the developed method.

Linearity:

Linearity was assessed directly on the drug substance by serial dilutions of standard stock solution. The calibration curve was plotted in Fig. 2. The curve was found to be linear over the concentration range of 5-35 µg/ml. The data was subjected to statistical analysis; the correlation coefficient was determined. The results were tabulated in table 3. The correlation coefficient (r^2) was found to

be 0.998 which has shown a good linearity between absorbance and concentration

Accuracy:

Accuracy of the method was determined in triplicate at three concentrations levels 50 %, 100 % and 150 % of target assay concentration. The results were expressed as the percentage of analyte recovered by the assay. The recovery of the drug from a series of spiked concentrations was presented in table 4. According to statistical data, the recovery of drug was found to be 99.28 % which was within the specified range of 98-102 %. Hence it can be concluded that the method was highly accurate for the determination of Gilteritinib fumarate.

Limit of Detection and Limit of Quantitation:

The detection limit was determined based on the standard deviation of y-intercepts and the slope from set of three calibration plots by using the following formulae.

LOD= 3.3× σ /s and LOQ=10× σ /s

Where, σ = the standard deviation of y-intercept of regression lines

s = the slope of the calibration curves

The LOD and LOQ of Gilteritinib fumarate were found to be 0.115 µg/ml and 0.349 µg/ml. The results of LOD and LOQ denote the sensitivity of the developed method.

Robustness:

Robustness of the developed method was established by deliberately changing the method parameters such as wave length (± 2 nm) and diluent ratio (± 5 %) to evaluate the impact on the method. A solution of target test concentration with the specified conditions was placed in the instrument and absorbance was noted in triplicate. The results were reported in the table 5 and found to be within the limits.

Assay of formulation:

Amount of drug present in the formulation was estimated by taking the standard as the reference. The average % assay was calculated and found to be 98.63 % for tablet formulation. Hence the method was successfully employed for assay of available formulation. The results were reported in the table 6.

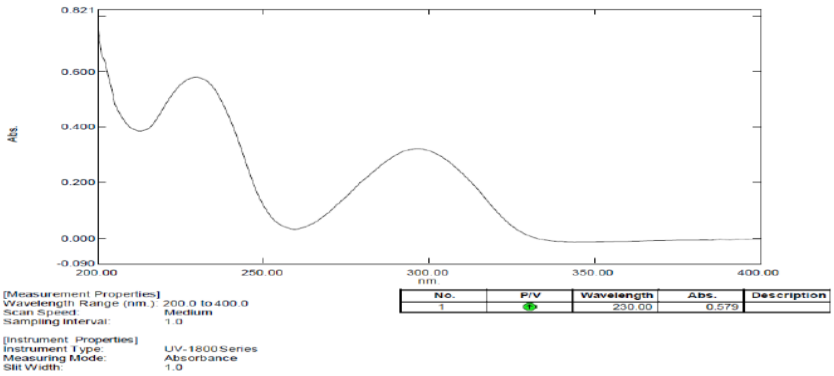

Fig. 1: UV spectrum of Gilteritinib fumarate

Table 1: RESULTS OF REPEATABILITY

S. No.	Concentration (µg/ml)	Absorbance
1	20	0.580
2	20	0.589
3	20	0.582
4	20	0.581
5	20	0.588
6	20	0.585
Mean		0.584
SD		0.004
RSD		0.6

Table 2: RESULTS OF INTERMEDIATE PRECISION

S. No.	Concentration (µg/ml)	Analyst 1	Analyst 2	Day 1	Day 2
1	20	0.578	0.564	0.574	0.564
2	20	0.574	0.569	0.576	0.567
3	20	0.577	0.560	0.573	0.563
4	20	0.579	0.563	0.575	0.569
5	20	0.572	0.561	0.578	0.565
6	20	0.576	0.568	0.570	0.560
	Mean	0.576	0.564	0.574	0.565
	SD	0.003	0.004	0.003	0.003
	RSD	0.5	0.6	0.5	0.5

SD=Standard Deviation; RSD= Relative Standard Deviation

Table 3: RESULTS OF LINEARITY

S. No.	Concentration (µg/ml)	Absorbance
1	5	0.127
2	10	0.254
3	15	0.398
4	20	0.560
5	25	0.702
6	30	0.842
7	35	1.012
Correlation coefficient		**0.998**

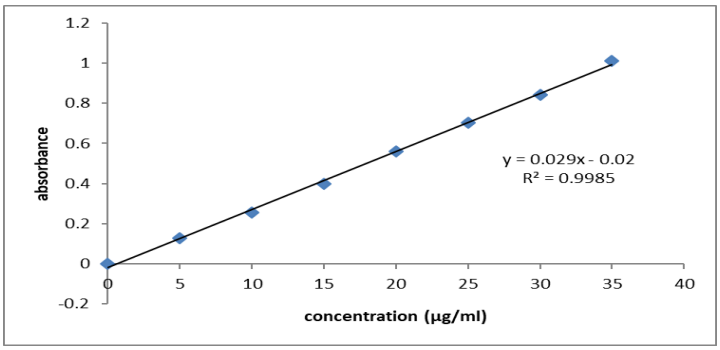

Fig. 2: LINEARITY CHART OF GILTERITINIB FUMARATE

Table 4: RESULTS OF ACCURACY

S. No.	Spiked level	Pre-analyzed sample conc. (µg/ml)	Amount added (µg/ml)	Total amount found (µg/ml)	% Recovery	% Mean Recovery*
1	50 %	20	10 10 10	9.827 9.896 10.034	98.28 98.97 100.34	99.28
2	100 %	20	20 20 20	19.758 20.068 20.172	98.79 100.34 100.86	
3	150 %	20	30 30 30	29.620 29.448 29.724	98.74 98.16 99.08	

*** represents means of nine observations**

Table 5: RESULTS OF ROBUSTNESS

Parameter	Gilteritinib fumarate	
	Absorbance*	RSD
Less wavelength (228 nm)	0.545	0.6
Actual wavelength (230 nm)	0.584	0.6
More wavelength (232 nm)	0.565	0.5
Changed diluent ratio (45:55)	0.564	0.6
Actual diluent ratio (50:50)	0.563	0.5
Changed diluent ratio (55:45)	0.574	0.6

*** represents means of six observations**

Table 6: RESULTS OF ASSAY FORMULATION

Formulation	Label claim (mg)	Concentr-ation of standard (µg/ml)	Average absorbance of standard solution*	Average absorbance of sample solution*	Amount of sample found (µg/ml)	% Assay
Gilteritinib fumarate Tablets	40	20	0.584	0.576	19.726	98.63

***Average of six experiments**

CONCLUSION

The proposed UV spectrophotometric method was found to be simple, accurate, precise, robust and economic for the estimation of Gilteritinib fumarate in bulk and pharmaceutical formulation. All the results obtained during validation were decorous in conjunction with acceptance criteria. Henceforth, the developed method can be used in quality control departments with respect to routine analysis for the assay of pure drug as well as the tablets containing Gilteritinib fumarate.

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Conflict of interests: Authors declare that no conflicts of interest exist in this research work.

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