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UV–SPECTROMETRIC DETERMINATION OF SORAFENIB TOSYLATE IN BULK AND PHARMACEUTICAL DOSAGE FORM

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ABSTRACT

A new, simple, economic and sensitive UV-spectrophotometric method was developed for the determination of Sorafenib in bulk and pharmaceutical formulations. The developed spectrometric method was validated for selectivity, linearity, range, precision, accuracy, ruggedness and sensitivity. The method has demonstrated excellent linearity over the range of 2-10 µg/ml with regression equation: y=0.079x-0.0081 and regression correlation coefficient r^2=0.999. The developed method demonstrated consistent high recoveries (97–99%) and low relative standard deviation (< 5%) at 265 nm. Moreover, the method was found to be highly sensitive with low limit of detection (0.028 µg/ml) and limit of quantitation (0.085 µg/ml). The apparent molar absorptivity and Sandell's sensitivity was found to be 48.09 $mol^{-1}cm^{-1}$ and 0.013245 $\mu g/cm^2$, respectively. The validated method was successfully employed for the drug content analysis from tablet preparations. Additionally, the method was also employed for pH metric solubility analysis of the drug.

Keywords: Sorafenib, Derivative UV Spectrophotometry, Pharmaceutical dosage form.

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INTRODUCTION:

Sorafenib Tosylate has the chemical name 4-{4-[[4-chloro-3-(trifluoro methyl) phenyl] carbamoyl amino] phenoxy}-N-methyl-pyridine-2-carboxamide, 4-methylbenzenesulfonate. Sorafenib Tosylate is a white to yellowish or brownish solid with a molecular formula of $C_{21}H_{16}ClF_3N_4O_3$, $C_7H_8O_3S$ and a molecular weight of 637.0 g/mole. Sorafenib tosylate is practically insoluble in water and Aqueous media but soluble in ethanol, methanol and PEG 400[1]. Sorafenib is an orally active multi tyrosine kinase inhibitor with anti-angiogenic effects. The drug is currently used orally (400mg bid) in the treatment of patients with advanced clear cell type renal cell carcinoma (RCC) and advanced hepatocellular carcinoma (HCC)[1]. There are various researches have done for this drug like Liquid chromatography-tandem mass spectrometry, HPLC using UV detector and MS but not much UV Spectrometric research has done[2,3,4]. So, there is a need for development of a simple, rapid, economic and sensitive assay of sorafenib. The proposed method is cheaper and simpler than other spectroscopic and chromatographic methods. It might be an alternative to the HPLC techniques for routine analysis and there are no extraction process to eliminate the excipients, which are time consuming and tedious.

MATERIALS AND METHODS

Instrument

A Shimadzu UV-1800 recording double beam UV–visible spectrophotometer with data processing system was used. UV spectra of reference and sample solutions were recorded in 1cm quartz cells at a scan speed of 50 nm/min with a fixed slit width of 3 nm. The concentration of Sorafenib is prepared in its solutions of methanol and were determined in the wavelength range of 265 nm.

Chemicals

The Purity of the sorafenib was tested by checking its melting point, UV and IR spectra and no impurities were found. All analytical chemicals were purchased from Merck. Stock solution of sorafenib (1000 µg/ml) was prepared in methanol. Standard solution was prepared by diluting the stock solution in the concentration range from 2.0 to 10.0 µg/ml with methanol.

Stock solutions

50 mg pure drug was dissolved in 50 ml methanol and 10 ml pipette out and diluted to 100 ml methanol as a standard solution. Firstly ten tablets were taken, weighed and powdered. An amount of this powder corresponding to one tablet Soranib content was weighed and transferred

to a 50 ml volumetric flask, sonicated for 10 mins and filtered using whatmann filter paper no. 41, then it is diluted to 100 ml methanol, these stock solutions were kept in the refrigerator by wrapping it with black cover for stability purpose from the stock solution different concentration of 2,4,6,8 and 10 µg/ml taken. The Zero order derivative UV spectra of the resulting solutions were recorded against methanol as a reference solution.

Stability

Sorafenib Tosylate is a stable substance and no sign of degradation is observed after 24 months of storage under ICH long term or accelerated conditions (12 months). The active substance was found to be resistant to heat, oxidation and hydrolysis. ICH light stability studies have been performed on sorafenib tosylate in the solid state and it was concluded to be stable. When dissolved in methanol it was shown to be slightly sensitive to light. Stability data was provided on three pilot scale batches of sorafenib tosylate micronized packaged in polyamide/polyethylene (PA/PE) bags [5]

RESULT AND DISCUSSION

Method Development

The solvent, the degree of derivation and the wavelength range were chosen in order to optimize the conditions. Sorafenib is not soluble in water, acid and base but completely soluble in methanol, ethanol and PEG 400 among these solvents methanol is taken as a sorafenib solution because it has suitable conditions with sorafenib. UV spectrum of Sorafenib in methanol gave broad peak with maximum wavelength at 265 nm. Derivative UV spectrophotometry was preferred for the analysis of Sorafenib since the amplitude of the signal of derivative spectra was greater, the peak shape was well defined and the separation of the shouldered peaks was better in this method. The Zero order derivative UV spectrum analysis of Sorafenib gave sharper and better-defined peaks when compared with the other derivative spectrum of Sorafenib.

VALIDATION PROCEDURES

The method validation was carried out according to the recommendations of analytical method validation.

Linearity

Calibration curve was analyzed on single day. The level of quality control was assayed once with standard curve. A linear regression was used to plot the peak area of sorafenib to absorbance *Vs* sorafenib concentration. The evolution of variance with respect to concentration, slope, intercept

and correlation coefficient were calculated for standard curve (Table.1), Regression correlation coefficient value is r^2=0.999. Graph of linearity studies is plotted (Figure 1)

Table 1: Absorbance Values for Calibration curve of Sorafenib Tosylate at 265 nm.

Sr. No.	Concentration (µg/ml)	Absorbance
1	2	0.152
2	4	0.293
3	6	0.449
4	8	0.612
5	10	0.782

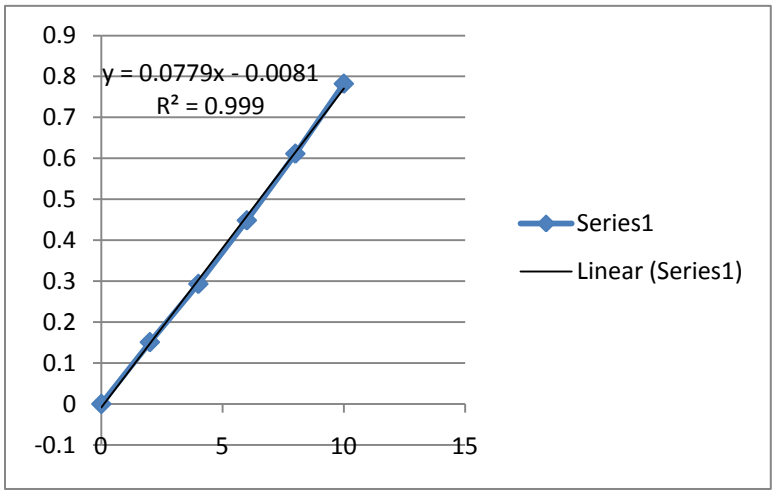

Figure .1 Calibration curve for Sorafenib Tosylate

Range

The range of an analytical procedure is the interval between the upper and lower concentration of analyte in the sample for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity, The range for this procedure is 2 to 10 µg/ml and it is selected on the basis of trial and error method.

Sensitivity

The limit of detection (LOD) was found to 0.028 µg/ml in methanol. The limit of quantitation (LOQ) of Sorafenib was 0.085µg/ ml in methanol.

Accuracy

Standard addition and recovery experiments were conducted to determine the accuracy of the proposed method. In order to detect interactions of the excipients in this method, the standard addition technique was applied to the same preparations that were analyzed by the calibration curve. The regression equation of standard addition curve was found as y =0.1019*x* - 0.0068

(r^2=0.9995). Where y is the amplitude of zero order derivative spectrums, x is concentration of Sorafenib and r is the coefficient of regression correlation

Recovery studies were performed at a concentration of 6 µg/ml Sorafenib standard solution in Methanol as 80, 100 and 120%. The recoveries were found to be 99.84, 98.46 and 97.16%, respectively and R.S.D. was found to be 0.167, 0.182 and 0.138, respectively. % Recovery was calculated (Table 2).Calibration curve for accuracy is plotted (Figure 2).

Table 2: Recovery study data of Sorafenib Tosylate by Zero order method

Sr. No	Amount of Drug Sample(µg)	Level of Recovery (%)	Amount Added (µg)	Amount Found (µg)	Recovery *(%)	SD*	%RSD
1	6	80	4.8	4.7784	99.84	0.1669	0.1672
2	6	100	6.0	5.9077	98.46	0.1791	0.1819
3	6	120	7.2	6.9871	97.16	0.1340	0.1379

*indicates average of six readings

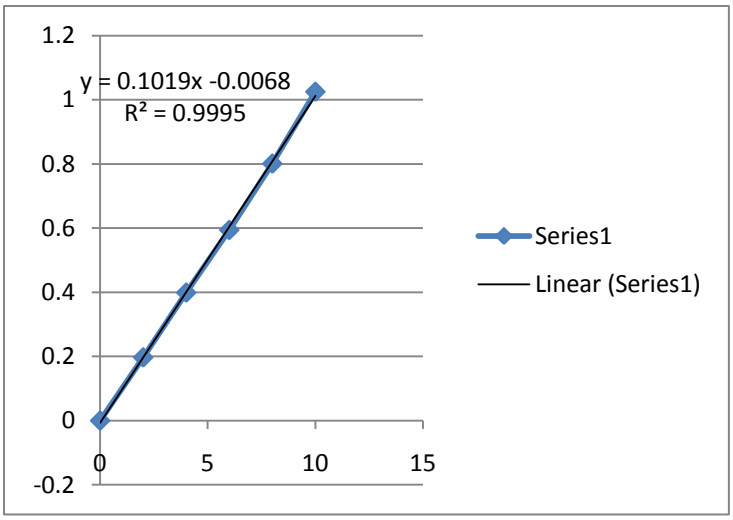

Figure 2 Calibration curve for Pharmaceutical Formulation

Precision

Intra and inter-day precision were evaluated at 2, 4, 6, 8 and 10 µg/ml. Six replicates of each concentration were assayed in one run for the intra-day experiment. Six replicates of each concentration were assayed within 6 different days for the inter-day experiment. The mean Sorafenib value was found as 6 µg/ml. The average S.D. of Intra-day precision was found to be 0.001 and that of Inter-day was found to be 0.003 (Table 3), suggesting that the developed method is a precise.

Ruggedness: The ruggedness test of analytical assay method is defined as degree of reproducibility of assay results obtained by the successful applications of the assay over time and among multiple laboratories and analyst. The ruggedness testing result is calculated (Table.4).

Table 3 Precision study data of Sorafenib Tosylate by Zero order spectroscopy

Concentration (µg/ml)	Intraday Absorbance Mean ± SD*	% RSD	Interday Absorbance Mean ± SD*	% RSD
2	0.156 ± 0.002	0.238	0.154	0.957
4	0.295 ± 0.002	0.661	0.293	1.550
6	0.450 ± 0.002	0.220	0.456	1.298
8	0.610 ± 0.003	0.060	0.611	0.851
10	0.783 ± 0.004	0.205	0.786	0.237

*indicates average of 6 readings

Table 4 Ruggedness study of Sorafenib by Zero order Spectroscopy

Analyst	Sample	Label claim(mg)	S.D.	%R.S.D.	Total amount Found
I	Soranib	200	0.1980	0.2015	196.55
II	Soranib	200	0.1608	0.1634	196.72

CONCLUSION:

An analytical Zero order derivative UV spectrophotometric method was developed and validated thoroughly for quantitative determination of Sorafenib in pure drug and tablets. The presented method was found to be rugged, simple, accurate, precise, reproducible and gives an acceptable recovery of the analyte, which can be directly and easily applied to the analysis of the pharmaceutical tablet formulations of Sorafenib.

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