Rapid Determination and Validation of Sorafenib via UV-Visible Method in Pharmaceutical Formulations

RAPID DETERMINATION AND VALIDATION OF SORAFENIB VIA UV-VISIBLE METHOD IN PHARMACEUTICAL FORMULATIONS

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ÖZ

GİRİŞ: Sorafenib en fazla kullanılan kinaz inhibitör ilaçlarındandır ve ilk olarak böbrek kanseri tedavisi için onay almıştır. Buna ek olarak ilaç karaciğer ve tiroid kanseri tedavisinde de kullanılmaktadır. Önerilen çalışma sorafenibin farmasötik preparatlarda tayinine yönelik yeni bir yöntemin geliştirilmesini hedeflemektedir.

GEREÇ VE YÖNTEM: Çalışmayı yürütmek üzere, referans standart numuneler temin edilip 0.5 – 25 µg/mL derişim aralığında 0.1 M HCl içeren metanol çözeltisinde hazırlanmıştır. Bütün çalışmalar 264 nm dalga boyunda UV-Görünür Bölge spektrofotometre cihazıyla yapılmıştır. Geliştirilen yöntem ICH kılavuzuna uygun olarak valide edilmiştir.

BULGULAR: Doğruluk ve kesinlik değerlerinin hem gün içi hem de günler arası verileri %4'ten daha iyi bulunmuştur. Yöntem kalibrasyon çözeltilerine bakıldığında lineerdir ve korelasyon katsayısı 0.9966 olarak hesaplanmıştır. Validasyon çalışması başarıyla tamamlandıktan sonra yöntem gerçek farmasötik formülasyonlar üzerinde uygulanmıştır ve bunun için Nevaxar preparatları yerel eczanelerden temin edilmiştir. Analitik geri kazanım çalışmaları standart ekleme yöntemine göre yapılmıştır. Üç farklı kalite kontrol çözeltisi bu çalışmalarda kullanılmıştır.

SONUÇ: Sonuç olarak geliştirilen ve geçerlilik testleri yapılan yöntemin farmasötik preparatların miktar analizinde başarıyla uygulanabilir olduğu yapılan çalışmalar sonucunda gözlenmiştir.

ANAHTAR KELİMELER: Validasyon, sorafenib, farmasötik formülasyon

ABSTRACT

INTRODUCTION: Sorafenib is one of the most preferred kinase inhibitor drug that formerly approved in order to apply on therapy for primary kidney cancer (advanced renal cell carcinoma). In addition to this, this drug get allowance for the treatment of primary liver cancer (hepatocellular carcinoma), and radioactive iodine resistant advanced thyroid carcinoma. This proposed work is achieved to suggest different procedure for determination of sorafenib in pharmaceutical formulations.

MATERIALS AND METHODS: In order to carry out the study, reference standard samples were kindly obtained and a working concentrations were prepared in methanol (0.5 – 25 µg/mL) including 0.1 M HCl. All measurements were organized via UV-Vis spectrophotometer at 264 nm wavelength. Developed method was validated following ICH guideline.

RESULTS: Precision and accuracy values for proposed method was found to be straightforwardly satisfactory whose values were better than 4% for both intra-day and inter day assays (n=6). Linearity was successively provided between working concentration and correlation coefficient that were calculated to be 0.9966. After all successful validation steps, method was applied to real pharmaceutical samples which kindly purchased by the local pharmaceutical store (Nevaxar). Analytical recovery study of the drug was calculated via standard addition method. Three different quality control solutions were used to perform proposed study.

CONCLUSION: To conclude, developed and validated method was successively applied on real samples by getting satisfactory results.

KEY WORDS: Validation, Sorafenib, Pharmaceutical Formulation

INTRODUCTION

In last, there were no successive pharmaceutical treatment for advanced refractory solid tumors that mostly finalized by death. Their survival rates for five years are almost low as 4-6% especially patients who suffered from liver, pancreatic and kidney cancers (1). Nevertheless, a new strategy were developed to cure this tumor via the advent of imatinib mesylate (2). After that time more than 30 different protein kinase inhibitors were developed to stop tumor development and progression offer promise for the future (3) . In accordance with clinical studies, the oral multikinase inhibitor, sorafenib, reduces tumor growth and disrupts tumor microvasculature through antiproliferative, antiangiogenic, and/or proapoptotic effects. Sorafenib exhibits antitumor activity in phase II/III trials including patients who suffer from advanced renal cell carcinoma and hepatocellular carcinoma. Its widespread preclinical and clinical activity could be explained by multiple molecular targets of sorafenib (the serine/threonine kinase Raf and receptor tyrosine kinases)(4).The Sorafenib active compound which is officially named by the IUPAC as 4-[4-[[4-chloro-3-(trifluoromethyl)phenyl]carbamoylamino]phenoxy]-N-methylpyridine-2-carboxamide. It mostly used for inhibition of oral multikinase enzyme that approved by the U.S. Food and Drug Administration in order to be chosen in therapy of several diseases which are advanced renal cell carcinoma (RCC) (5, 6), thyroid carcinoma and hepatocellular carcinoma (HCC) (7, 8). This drug was also get approval from the European Medicines Agency for patients who suffer from HCC and patients with advanced RCC where other severe therapy models did not work or those considered having allergy for such therapy. 400 mg is accepted as the recommended daily taken amount. Tablets containing sorafenib tosylate (274 mg) which equals to 200 mg of sorafenib. Pharmaceutical tablets are round, biconvex, red film-coated tabletsThe efficiency of sorafenib was also evaluated for some solid tumors like melanoma and different types of lung cancer (9-11). It is observed that significant increase was provided in overall survival via sorafenib-administered patients with advanced HCC in a phase III, placebo-controlled experiments represents an impressive results in the management of this complex disease, which was the first reported case that suggest a therapy without systemic treatment options (11). It is reported that Sorafenib is contraindicated in patients who suffer from severe hypersensitivity(12). In addition to this, simultaneous administration of drug with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer(13). Adverse reactions reported for Sorafenib administraiton were diarrhea in 55% (grade 3, 10%), hand–foot syndrome in 21% (grade 3, 8%), rash in 19% (grade 3, 1%), and cardiac ischemia or infarction in 2.7% (versus 1.3% for placebo)(14).

As its importance increases due to different applications on several solid tumors, analytical interest is also raise up to this pharmaceutical (15-18). In this study, the main goal of the proposed work is developing and validating a novel quantitative method for evaluating the concentration of sorafenib in both bulk and pharmaceutical formulations via UV-Vis spectrophotometric method.

MATERIAL AND METHODS

Chemicals and Reagents

Sorafenib reference material, methanol and HCl chemicals were purchased from Sigma & Aldrich. Pharmaceutical formulations were kindly obtained from local pharmacy store.

Apparatus

All spectrophotometric measurements were performed via Thermo Scientific MultiSkan Go model UV-VIS spectrophotometer that has a diode array feature (DAD) (190 - 1100 nm). Both standards and real samples were located on 96 well plates and the data recorded at the wavelength from 190 to 350 nm.

Standard solutions

Reference standard of Sorafenib (1 mg/mL) was prepared in methanol (1% HCl v/v) and stored in a place that protect the samples from the light at +4°C .All working samples were daily prepared from the stock that was already prepared from the reference at the concentrations of 0.50 - 25.00 µg/mL in methanol. Then the absorbances of these solutions were recorded. Quality control solutions were also prepared by the same methods.

Tablet solutions

Twelve tablets of Nevaxar © were kindly weighed and finely powdered. Sample was taken which was equal to the average amount of single tablet. These aliquots were transferred into a 100 mL volumetric flask. Then 25 mL of solvent (methanol including %0.1 HCl) was added into the solid powder. Finally, obtained mixture was sonicated about 15 min to form a perfect dissolution of active compound and then solution diluted to expected volume

(100 mL) with methanol-HCl mixture. A centrifugation process was carried out about 15 min at 5000 rpm for filtering the undesired excipients. Suitable solutions were prepared from obtained clear supernatant and diluting them with methanol-HCl mixture to get final concentration (4 µg/mL). Ultimately, these prepared samples were mixed with quality control solutions in order to perform standard addition method to investigate analytical recovery performance of the proposed method. The amount of active substance in a single tablet was measure by the calibration curve of standard samples.

RESULTS AND DISCUSSION

Diode Array Detector on UV-Vis Spectrophotometer makes it possible to scan the whole spectrum. In accordance with the basic scan, it is observed that sorafenib has a maximum at 264 nm wavelength. All measurements were recorded on this data.

Validation

Validation is an essential part of quality assurance. Validated methods provide a high degree of assurance that uniform batches were generated with required specifications. All analysis are formally approved. It is a formal obligation to approve the afety of any methods. Several validation parameters were taken into account to exhibit the applicability of the proposed method. The examined validation parameters which were linearity, sensitivity, precision, accuracy, recovery, specificity, were considered in developed method. These parameters showed that proposedmethod could be applicable on analysis of Sorafenib in both bulk and pharmaceutical formulations

Linearity

In this study, the calibration graphs was plotted via absorbance versus concentration. A linearity were observed over the range of 0.50 - 25.00 µg/mL for suggested method. The calibration graphs for the sorafenib were successfully plotted by evaluating the results of 9 different samples Calibration graph were plotted by calculating the mean value of three independent measurements for each pre-determined concentration. Table I exhibited both correlation coefficient and regression equation while calibration curve were mentioned in Figure 2. In figure 1 the overlapped of each point were showed.

Figure 1. Overlapped spectra for sorafenib (0.5-25 µg/mL)

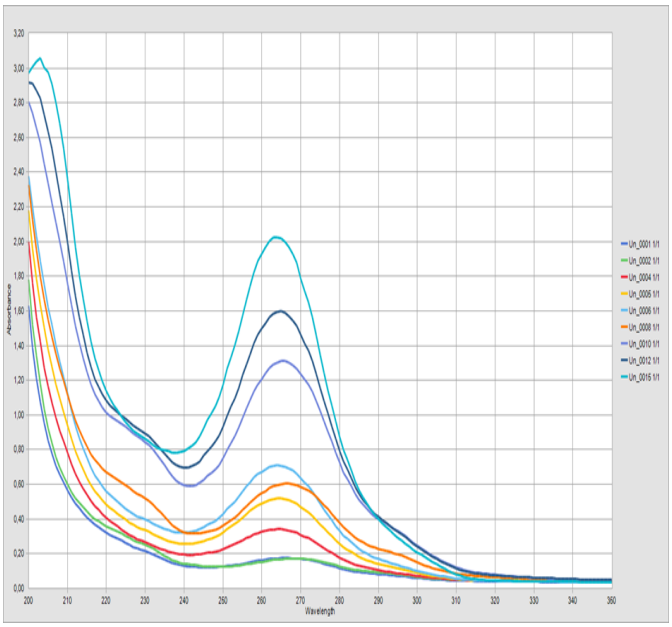
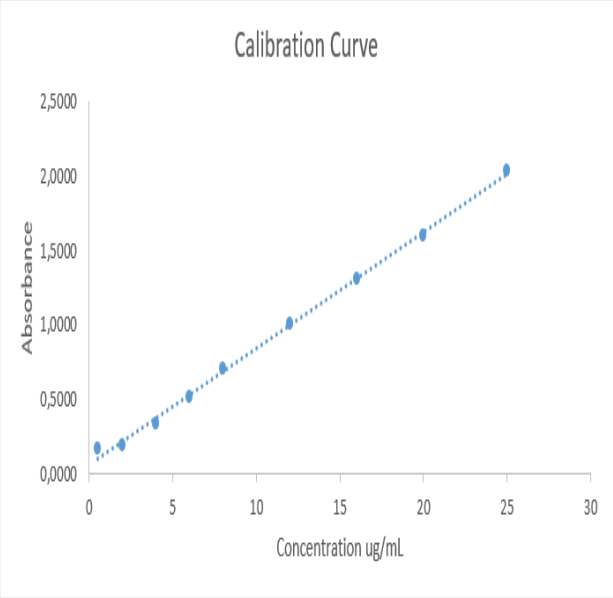


Table 1. *Statistical parameters for calibration curve of Sorafenib*

Parameters	*UV-Vis Method*
Regression Equation	*y = 0.0775x + 0.0773**
Standard Error of Slope (STHYX)	*1.1×10^{-2}*
Standard Error of Intercept	*1.6×10^{-2}*
Correlation Coefficient	*0.9976*
Linearity Range (µg/mL)	*0.5-25*
Number of Data Points	*9*

Figure 2. *Calibration Curve for Sorafenib.*



Sensitivity

The limit of quantification (LOQ) is described as the lowest concentration of Sorafenib that could be determined by admissible precision and accuracy value. This value could be calculated by the deviation of the slope of the curve. The LOQ was calculated to be 0.34 µg/mL for proposed method while Limit of Detection (LOD) was found to be 0.1 µg/mL.

Precision

The precision in drug analysis is simply described as the statistical point of view for the repeated independent test results for a proposed method. Three different concentrations, quality controls, of reference in the linear range (1.50, 10.00 and 18.00 µg/mL) were determined in 3 independent series in both the present day (intra-day precision) and 3 following days (inter-day precision) from three different measurements of quality controls. The precision value of the current study was recorded by calculating the relative standard deviation (RSD %). The RSD results of both intra and inter day experiments indicated that precision of the study is better than 3.89 % and the intermediate precision of the study was found to be acceptable. (Table 2).

Table 2. *Precision values for validation of Sorafenib*

Drug	(nm)	Added (µg/mL)	Intra-Day		Inter Day	
			Mean±SD (µg/mL)	Precision %RSD	Mean±SD (µg/mL)	Precision % RSD
Sorafenib	264	1.50	1.51±0.003	1.65	1.48±0.007	3.89
		10.00	10.38±0.010	1.16	10.16±0.015	0.14
		18.00	17.83±0.018	1.29	18.20±0.021	1.44

Accuracy

Accuracy is described as the closeness of the result with respect to the real amount. In this study 6 different aliquots of 3 Quality control samples (1.5, 10 and 18 µg/mL) were under interest. Satisfactory results were obtained for both intra-day and intraday assays. Accuracy results were found to be better than 3.76. Statistical parameters were monitored in Table 3. Spectra of Quality control samples were observed in Figure 3.

Figure 3. *Overlapped Spectra for Quality Control Samples*

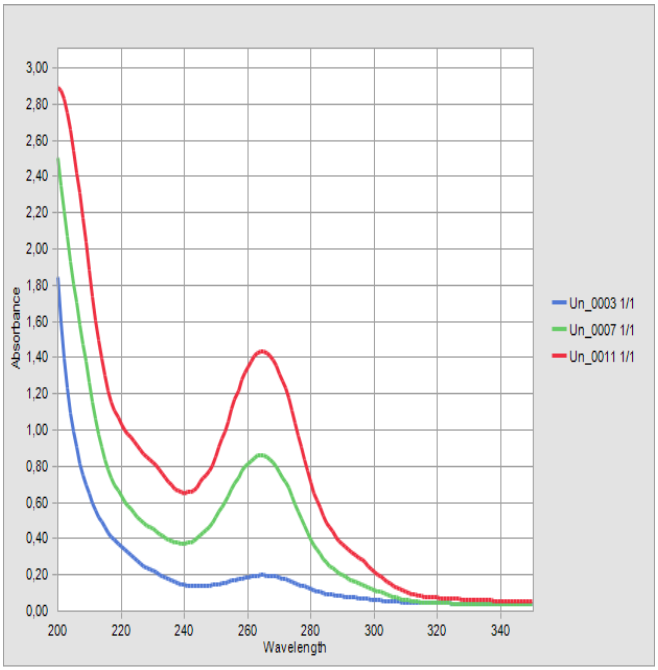


Table 3. *Accuracy values for validation of Sorafenib*

Drug	(nm)	Added (µg/mL)	Intra-Day		Inter Day	
			Mean±SD (µg/mL)	Precision %RSD	Mean±SD (µg/mL)	Precision % RSD
Sorafenib	264	1.50	1.51±0.003	0.82	1.48±0.007	-1.15
		10.00	10.38±0.010	3.76	10.16±0.015	1.60
		18.00	17.83±0.018	-0.95	18.20±0.021	1.12

Specificity

A blank solution was measured between 190-350 nm and there is no interference observed during the analysis. Also major excipients were dissolved in methanol HCl mixture and the proposed method was applied to excipients. Any overlapping absorbance recorded along the analysis. Therefore, it is noticed that method is specific for determination of Sorafenib in bulk and pharmaceutical formulations.

Analysis of pharmaceutical formulations

The developed spectrophotometric method was directly administered to the pharmaceuticals neither derivatisation nor filtration. Obtained data strongly revealed that developed method may trustfully be applied for the quantitative evaluation of Sorafenib in its tablet from. Standard addition method is followed for this assay in order to avoid potential matrix effect. The mean Analytical Recovery of the pharmaceutical is found to be 100.8% ± 0.3.

CONCLUSION

In this study, a UV-Vis spectrophotometric method that is simple, rapid and convenient was optimised and validated for the quantitative evaluation of Sorafenib in bulk and pharmaceutical formulations. This method was kindly carried out to the determination of pharmaceutical dosage forms neither necessity for derivatisation nor complicated sample preparation steps. Furthermore this proposed method has the lowest LOD and LOQ values for spectrophotometric analysis. Thus, linear range is more sensitive than the other published derivative spectrophotometric method. According to the current data, it is claimed that the method exhibited high sensitivity, accuracy, precision. In addition to this advantages, method is relatively simple and cheap with respect to the other chromatographic measurements. It could be applied for the routine analysis of Sorafenib in pharmaceutical formulations for quality control centers and clinics.

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