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Analytical estimation methods for determination of sorafenib

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Abstract

Sorafenib is an anticancer drug is used to treat late stage kidney and liver cancer. Sorafenib is used to treat advanced renal cell carcinoma (RCC; a type of cancer that begins in the kidneys). Sorafenib is also used to treat hepatocellular carcinoma (a type of liver cancer) that cannot be treated with surgery and a certain type of thyroid cancer that has spread to other parts of the body and cannot be treated with radioactive iodine. Sorafenib is in a class of medications called kinase inhibitors. It works by blocking the action of an abnormal protein that signals cancer cells to multiply. This helps stop the spread of cancer cells. There are many reported analytical methods for estimation of Sorafenib. The present work list outs the various analytical methods for the estimation of the drug.

Keywords: Sorafenib; Antineoplastic agent; Estimation methods; Review

1. Introduction

Sorafenib is chemically 4-[4-[[4-chloro-3-(trifluoromethyl)phenyl]carbamoylamino] phenoxy]-N-methyl-pyridine-2-carboxamide, Sorafenib (rINN), marketed as Nexavar by Bayer, is a drug approved for the treatment of advanced renal cell carcinoma (primary kidney cancer). It has also received "Fast Track" designation by the FDA for the treatment of advanced hepatocellular carcinoma (primary liver cancer), and has since performed well in Phase III trials. Sorafenib is a small molecular inhibitor of Raf kinase, PDGF (platelet-derived growth factor), VEGF receptor 2 & 3 kinases and c Kit the receptor for Stem cell factor. A growing number of drugs target most of these pathways.

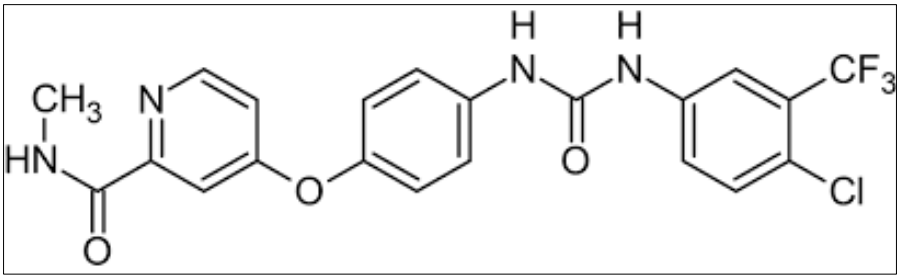

Figure 1 Structure of Sorafenib

The originality of Sorafenib lays in its simultaneous targeting of the Raf/Mek/Erk pathway. Its side effects are bleeding gums, blistering, peeling, redness, or swelling of the palms of the hands or bottoms of the feet, bloating of the abdomen

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or stomach, blood in the urine or stools, clay-colored stools, coughing up blood, difficulty with breathing or swallowing. Its pKa (Strongest Acidic)-7.2, pKa (Strongest Basic) 15.04, Its Molecular formula is $C_{21}H_{16}ClF_3N_4O_3$. Molecular Weight. 464.8g /mol. Sorafenib tosylate is insoluble in water; however, it is soluble in DMSO and ethanol, Molecular Formula for tosylate form is $C_{28}H_{24}ClF_3N_4O_6S$, Molecular Weight is 637.0 g/mol. Its structure is shown in Fig. 1.

2. Various Analytical methods

2.1. HPLC Methods

The current research work envisages an analytical quality by design-enabled development of a simple, rapid, sensitive, specific, robust and cost-effective stability-indicating reversed-phase high-performance liquid chromatographic method for determining stress-induced forced-degradation products of sorafenib tosylate (SFN). An Ishikawa fishbone diagram was constructed to embark upon analytical target profile and critical analytical attributes, i.e. peak area, theoretical plates, retention time and peak tailing. Factor screening using Taguchi orthogonal arrays and quality risk assessment studies carried out using failure mode effect analysis aided the selection of critical method parameters, i.e. mobile phase ratio and flow rate potentially affecting the chosen critical analytical attributes. Systematic optimization using response surface methodology of the chosen critical method parameters was carried out employing a two-factor–three-level–13-run, face-centered cubic design. A method operable design region was earmarked providing optimum method performance using numerical and graphical optimization. The optimum method employed a mobile phase composition consisting of acetonitrile and water (containing orthophosphoric acid, pH 4.1) at 65:35 v/v at a flow rate of 0.8 mL/min with UV detection at 265 nm using a C18 column. Response surface methodology validation studies confirmed good efficiency and sensitivity of the developed method for analysis of SFN in mobile phase as well as in human plasma matrix. The forced degradation studies were conducted under different recommended stress conditions as per ICH Q1A (R2). Mass spectroscopy studies showed that SFN degrades in strongly acidic, alkaline and oxidative hydrolytic conditions at elevated temperature, while the drug was per se found to be photostable. Oxidative hydrolysis using 30% H2O2 showed maximum degradation with products at retention times of 3.35, 3.65, 4.20 and 5.67 min. The absence of any significant change in the retention time of SFN and degradation products, formed under different stress conditions, ratified selectivity and specificity of the systematically developed method[1].

To develop and validate a simple ultrafast monolithic high performance liquid chromatography (HPLC) method for the simultaneous quantification of two anti-cancer agents, imatinib and sorafenib, in pure form and tablet preparations. Chromatographic separation was accomplished using Chromolith flash RP-18 HPLC-column (25 - 4.6 mm; macropores, 2 µm; mesopores, 13 – 15 nm). The optimum mobile phase composition of ammonium acetate buffer (10 mM, pH 8.5) and methanol at ratio of 35:65 v/v was used. Effluent flow rate was adjusted to 1.0 mL/min and the analysis was performed at 250 nm wavelength. The developed method was evaluated for specificity, linearity, precision and accuracy. The method offered a linear relationship over the concentration range of 1 - 16 µg/ml (correction coefficient, R2 = 0.9999) for both analytes. Limit of detection (LOD) was 0.1891 and 0.1888 µg/ml while limit of quantification (LOQ) was 0.6303 and 0.6294 µg/ml for imatinib and sorafenib, respectively. Mean recovery was within 100 ± 2 %. The utility of the new method was demonstrated by its successful use for the analysis of commercially available tablet formulations of both drugs. The developed method is fast and economical, and is being recommended for routine analysis of imatinib and sorafenib in bulk drug and tablet dosage forms in quality control laboratories[2].

Sorafenib is recommended for therapy of advanced hepatocellular carcinoma and renal cell carcinoma. Preclinical data indicate a relation between dose and antitumor efficacy. In clinical trials, adverse events improve after dose reduction suggesting a dose-dependent toxicity. Given dose has a direct impact on the drug serum concentration, but the latter also can be influenced by multiple factors, including interaction and metabolisation. To enable the investigation of concentration-related effects, an easy and sensitive assay for sorafenib drug monitoring is essential. A high-performance liquid chromatography (HPLC) analysis involving an extraction with diethyl ether followed by separation on a Pinnacle™ DB C18 column and quantitation by UV absorbance at 260 nm was established. Sorafenib concentrations in samples of serum and peritoneal fluid have been determined. The assay was validated for serum samples and is linear over the concentration range of 100–5,000 ng/ml with a determination coefficient of >0.999. The limit of detection is 0.25 ng/ml. The intra- and inter-day coefficients of variation were below 3.03%. Sorafenib recovery in spiked probes of peritoneal fluid was above 85%. Sorafenib concentrations in 44 serum samples and 14 probes of peritoneal fluid have been determined with a mean of 3,328 and 1,380 ng/ml, respectively (standard deviation 2,267 and 659 ng/ml). A sensitive and selective HPLC method for the determination of sorafenib in human serum was developed and also verified for peritoneal fluid. This method provides a useful tool for pharmacokinetic investigations as well as for therapeutic drug monitoring of sorafenib[3].

To develop a simple, novel, sensitive and rapid reverse phase high performance liquid chromatographic method for simultaneous determination of paclitaxel, sorafenib and omeprazole in standard solutions and spiked human plasma and its application to the in-vitro and in-vivo evaluation of paclitaxel polymeric nanoparticle formulations. The method was tested for the assessment of paclitaxel, omeprazole and sorafenib using tamoxifen citrate as internal standard. The analysis was performed at a wavelength of 235 nm using Thermo HS C18 column, 40 °C column oven temperature, acetonitrile and water (70:30 v/v, pH 3.37 adjusted with phosphoric acid) as a mobile phase and at a flow rate of 0.8 ml/min. All analytes were extracted by simple protein precipitation method using acetonitrile. The linearity was assessed in the concentration range of 1 - 2000 ng/mL for paclitaxel, omeprazole and sorafenib. The developed chromatographic method effectively separated omeprazole, paclitaxel, sorafenib and IS with retention time of 3.93, 5.18, 6.43 and 9.93 min, respectively. The chromatograms of the three target compounds and IS showed good resolution and peak separation. The LOD of the method was 1, 5 and. 5 ng/mL while the LOQ was 2, 7.5 and 10 ng/mL, for paclitaxel, sorafenib and omeprazole, respectively. The proposed RP-HPLC–UV method for the assessment of paclitaxel, sorafenib and omeprazole in standard solutions and spiked plasma is simple, economical, sensitive and robust. The method is also suitable for the analysis of paclitaxel in nano formulations and for its pharmacokinetic studies in an animal model[4].

Since decades, the plant bioactives have shown tremendous promise in the therapeutic management of cancer. Lately, many synthetic drugs and natural bioactive molecules have been used in combination for potential synergism in cancer therapeutics. Sorafenib (SFN) and chrysin (CHR) form one of such promising combinations with definitive synergistic potential in cancer therapy. This has, however, given rise to analytical challenges, as it becomes quite difficult to identify and quantify two or more active moieties simultaneously in the presence of each other. Herein, we report the development and validation of an HPTLC densitometric method for analysis of SFN and CHR, in combination, followed by studying the effect of biological matrix (i.e., plasma), on the assay of both the molecules. Solvent system, comprising of toluene: n-hexane: isopropyl alcohol (7:2:1), was employed for chromatographic separation with Rf values of 0.3 and 0.5, for SFN and CHR, respectively. Validation studies established linearity for the concentrations ranging from 20 to 800 ng/band for each of the molecules, along with high degree of accuracy, precision (intra- and inter-day), ruggedness, robustness, and sensitivity of the liquid chromatographic method. Specificity studies using plasma as the biological matrix, exhibited well-resolved peaks of both the molecules, coupled with high recovery values too. The aforesaid method was finally applied to the estimation of real plasma levels in Wistar rats, following co-administration of SFN and CHR as a suspension. In a nutshell, the validated analytical method can be productively applied for simultaneous estimation of SFN and CHR, for routine analysis, in drug formulations and in biological matrices like plasma[5].

A rapid and simple liquid chromatography-UV spectrometric assay was developed for the quantitative determination of sorafenib in the presence of cationic and anionic PAMAM dendrimers. PAMAM dendrimer:sorafenib (SFB) admixture was prepared by Higuchi rotating bottle method for different generations (G4, G4.5, G5). Separation was achieved on a C18 column (Knauer Eurospher 150 mm × 4.6 mm with precolumn) at room temperature using an isocratic elution method with acetonitrile/K-phosphate buffer 25 mM pH 7.4: 55/45 (v/v) at a flow rate of 1.5 ml/min. The SFB peak was separated well from PAMAM dendrimers peak. Calibration curves were linear in the concentration range of 0.097–100 mcg/mL with R2 > 0.9988. The accuracy [Bias (%)] and precision [RSD (%)] values, calculated from three different sets of quality control samples analyzed in triplicate on four different days, ranged from −3.6–16 and 2.1–14.5, respectively. The limit of quantitation was 97 ng/mL[6].

A simple, accurate, specific reverse-phase, high-performance liquid chromatography method has been developed for the determination of sorafenib tosylate in its pure form and its tablets. In this method, sorafenib tosylate was eluted by isocratic mode using a Phenomenex Luna C18 column by a mobile phase composition of acetonitrile and water in the ratio of 82.5: 17.5, v/v. The flow rate was 1.5 mL/min. The eluted drug was monitored at 265 nm and the method was found to be linear from 5 to 80 µg/mL. The method was validated by linearity, precision, accuracy, LOD, and LOQ. The accuracy report denotes that there is not any interference of additives used in the formulation[7].

Sorafenib, a new oral multikinase inhibitor with antiangiogenic properties, has demonstrated preclinical and clinical activity against several tumor types. The aims of this study were to validate a method for the measurement of sorafenib in plasma from cancer patients, then to test this method in clinical practice. Following liquid–liquid extraction, the compounds were separated with gradient elution (on a C18 ultrasphere ODS column using a mobile phase of acetonitrile/20 mM ammonium acetate), then detected at 255 nm. The calibration was linear in the range 0.5–20 mg/L. Intra- and inter-assay precision was lower than 7 and 10%, respectively, at 0.5, 3 and 20 mg/L. Plasma sorafenib concentrations were measured in 22 cancer patients (99 samples). The mean trough sorafenib concentration (Cmin) and concentration at peak were 4.3 ± 2.5 mg/L (n = 68, CV = 57.5%) and 6.2 ± 3.0 mg/L (n = 31, CV = 47.5%), respectively. Mean sorafenib Cmin in eight patients who experienced grade 3 drug-related adverse events was approximately 1.5-fold greater than that observed in the remaining patients (7.7 ± 3.6 mg/L vs. 4.4 ± 2.4 mg/L, P = 0.0083). In conclusion, the method was successfully used in routine practice to monitor plasma concentrations of

sorafenib in cancer patients. Finally, large interindividual variability and higher exposure in patients experiencing severe toxicity support the need for therapeutic drug monitoring to ensure an optimal exposure to sorafenib[8].

A rapid and sensitive liquid chromatography/tandem mass spectrometric (LC/MS/MS) assay wasdeveloped for the quantitative determination of sorafenib in human plasma. Sample pretreatment involved simple protein precipitation by the addition of 0.5 mL acetonitrile, containing internal standard ([2H3, 15N] sorafenib), to 50 µL of plasma sample volume. Separation was achieved on a Waters SymmetryShield RP8 (2.1×50 mm, 3.5 µm) column at room temperature using an isocratic elution method with acetonitrile/0.1% formic acid in water: 65/35 (v/v) at a flow rate of 0.25 mL/min. Detection was performed using electrospray ionization in positive ion Multiple Reaction..Monitoring (MRM) mode by monitoring the ion transitions from m/z 464.9→ 252.0 (sorafenib) andm/z 469.0→259.0 (internal standard). Calibration curves were linear in the concentration range of 5–2000 ng/mL. The accuracy and precision values, calculated from three different sets of quality control samples analyzed in quintuplicate on six different days, ranged from 92.86–99.88 % and from1.19–4.53 %, respectively[9].

A sensitive, rapid, precise, accurate high-performance liquid chromatographic method was developed for the estimation of Sorafenib (SOR) in the tablet dosage form. Chromatographic separation of SOR was carried out utilizing thermo-scientific model C18 column (4.6 mm i.d. X 250 mm; 5µm particle size) (based on 99.99 % ultra-high purity silica) using mobile phase that consisting of acetonitrile: methanol (40:60 v/v) at a flow rate of 1.0 mL/min. The absorption maximum (λmax) of SOR in the mobile phase was found to be 265.5 nm. It had a retention time of 3.223 min. The calibration curve was in linear function of the drug in the concentration range of 2-10 µg/mL (r2 = 0.999) for the optimized method. The regression equation for SOR was found to be Y = 68228 x + 8071. The Detection Limit (DL) & Quantitation Limit (QL) results of SOR were found to be 0.526 µg/mL and 1.594 µg/mL respectively. The developed method was validated in pursuance of ICH Q2 (R1) guidelines. The method was linear, precise, accurate with recoveries in the range of 98 - 102 %, and minimum values of % RSD indicate the accuracy of the method. The detailed quantitative results of the study show that this method is precise, accurate, and cost-effective. Thus, the developed RP-HPLC method can be successfully feasible for the routine quality control analysis of SOR in a pharmaceutical dosage form[10].

The current research work envisages an analytical quality by design-enabled development of a simple, rapid, sensitive, specific, robust and cost-effective stability-indicating reversed-phase high-performance liquid chromatographic method for determining stress-induced forced-degradation products of sorafenib tosylate (SFN). An Ishikawa fishbone diagram was constructed to embark upon analytical target profile and critical analytical attributes, i.e. peak area, theoretical plates, retention time and peak tailing. Factor screening using Taguchi orthogonal arrays and quality risk assessment studies carried out using failure mode effect analysis aided the selection of critical method parameters, i.e. mobile phase ratio and flow rate potentially affecting the chosen critical analytical attributes. Systematic optimization using response surface methodology of the chosen critical method parameters was carried out employing a two-factor–three-level–13-run, face-centered cubic design. A method operable design region was earmarked providing optimum method performance using numerical and graphical optimization. The optimum method employed a mobile phase composition consisting of acetonitrile and water (containing orthophosphoric acid, pH 4.1) at 65:35 v/v at a flow rate of 0.8 mL/min with UV detection at 265 nm using a C18 column. Response surface methodology validation studies confirmed good efficiency and sensitivity of the developed method for analysis of SFN in mobile phase as well as in human plasma matrix. The forced degradation studies were conducted under different recommended stress conditions as per ICH Q1A (R2). Mass spectroscopy studies showed that SFN degrades in strongly acidic, alkaline and oxidative hydrolytic conditions at elevated temperature, while the drug was per se found to be photostable. Oxidative hydrolysis using 30% H2O2 showed maximum degradation with products at retention times of 3.35, 3.65, 4.20 and 5.67 min. The absence of any significant change in the retention time of SFN and degradation products, formed under different stress conditions, ratified selectivity and specificity of the systematically developed method[11].

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sensitive and selective HPLC method for the determination of sorafenib in human serum was developed and also verified for peritoneal fluid. This method provides a useful tool for pharmacokinetic investigations as well as for therapeutic drug monitoring of sorafenib[12].

2.2. LC-MS Methods

Rapid, sensitive and specific method was developed and validated using LC/MS/MS for determination of sorafenib in human plasma. Sample preparation involved a single protein precipitation step by the addition of 0.1 mL of plasma with 0.5 mL acetonitrile. Analysis of the compounds of interest including the internal standard ([2H3 15N] sorafenib) was achieved on a Waters X-Terra™ C18 (150 mm × 2.1 mm i.d., 3.5 μm) analytical column using a mobile phase consisting of acetonitrile/10 mM ammonium acetate (65:35, v/v) containing 0.1% formic acid and isocratic flow at 0.2 mL/min for 6 min. The analytes were monitored by tandem mass spectrometry with electrospray positive ionization. Linear calibration curves were generated over the range of 7.3–7260 ng/mL for the human plasma samples with values for the coefficient of determination of >0.96. The values for both within day and between day precision and accuracy were well within the generally accepted criteria for analytical methods (<15%)[13].

In this study, a controlled drug release system based on redox-responsive nanomicelles for drug delivery was described. The system was constructed by linking poly (acryic acid) (PAA) with D-α-tocopherol succinate (VES) via a disulfide bond linker (ss). This amphiphilic polymer (PAAssVES) was synthesized by coupling reaction and its chemical structure was confirmed by FT-IR and 1HNMR analyses. PAAssVES was found to self-assemble into nanomicelles with diameter of about 130 nm, and a critical micelle concentration of about 6.3 μg/mL. The Sorafenib-loaded nanomicelles (SFN-NM) were almost spherical as observed by transmission electron microscopy. Differential scanning calorimetry analysis showed that Sorafenib (SFN) was entrapped in the micelles in an amorphous or molecular state. The safety of SFN-NM was confirmed by he molysis study. The release of SFN from the nanomicelles was dependent on the concentration of glutathione (GSH), with 85% of the drug being released under the maximum concentration (40 mM) of GSH used. SFN-NM exhibited stronger cytotoxicity than free SFN against BGC-823 cells under the same SFN concentration. Furthermore, pharmacokinetics study showed that the bioavailability of SFN in rat obtained by injecting the animal with SFN-NM was about 2.8-fold the bioavailability of SFN obtained by injecting the animal with free SFN. Thus, the redox-responsive SFN delivery system described in the current study could be considered as a carrier for delivering SFN.In this study, a controlled drug release system based on redox-responsive nanomicelles for drug delivery was described. The system was constructed by linking poly (acryic acid) (PAA) with D-α-tocopherol succinate (VES) via a disulfide bond linker (ss). This amphiphilic polymer (PAAssVES) was synthesized by coupling reaction and its chemical structure was confirmed by FT-IR and 1HNMR analyses. PAAssVES was found to self-assemble into nanomicelles with diameter of about 130 nm, and a critical micelle concentration of about 6.3 μg/mL. The Sorafenib-loaded nanomicelles (SFN-NM) were almost spherical as observed by transmission electron microscopy. Differential scanning calorimetry analysis showed that Sorafenib (SFN) was entrapped in the micelles in an amorphous or molecular state. The safety of SFN-NM was confirmed by hemolysis study. The release of SFN from the nanomicelles was dependent on the concentration of glutathione (GSH), with 85% of the drug being released under the maximum concentration (40 mM) of GSH used. SFN-NM exhibited stronger cytotoxicity than free SFN against BGC-823 cells under the same SFN concentration. Furthermore, pharmacokinetics study showed that the bioavailability of SFN in rat obtained by injecting the animal with SFN-NM was about 2.8-fold the bioavailability of SFN obtained by injecting the animal with free SFN. Thus, the redox-responsive SFN delivery system described in the current study could be considered as a carrier for delivering SFN[14].

A rapid and sensitive liquid chromatography/tandem mass spectrometric (LC/MS/MS) assay was developed for the quantitative determination of sorafenib in human plasma. Sample pretreatment involved simple protein precipitation by the addition of 0.5 mL acetonitrile, containing internal standard ([2H3, 15N] sorafenib), to 50 μL of plasma sample volume. Separation was achieved on a Waters SymmetryShield RP8 (2.1 mm × 50 mm, 3.5 μm) column at room temperature using an isocratic elution method with acetonitrile/0.1% formic acid in water: 65/35 (v/v) at a flow rate of 0.25 mL/min. Detection was performed using electrospray ionization in positive ion multiple reaction monitoring (MRM) mode by monitoring the ion transitions from m/z 464.9 → 252.0 (sorafenib) and m/z 469.0 → 259.0 (internal standard). Calibration curves were linear in the concentration range of 5–2000 ng/mL. The accuracy and precision values, calculated from three different sets of quality control samples analyzed in quintuplicate on six different days, ranged from 92.86% to 99.88% and from 1.19% to 4.53%, respectively[15].

Targeted therapies such as cabozantinib (CABO), pazopanib (PAZO), sorafenib (SORA), sunitinib (SUNI) and its main active metabolite N-desethyl-sunitinib (DST-SUNI), olaparib (OLA) and palbociclib (PALBO) display large pharmaco kinetics variability impacting their responses in terms of efficacy or toxicity. For the monitoring of these drugs, an analytical method allowing to routinely measure their concentrations in human plasma is needed. Such a method has been developed and validated and is presented here. The chromatographic separation is achieved on a Zorbax Bonus-

RP analytical column using an isocratic elution of 92% V/V of acetonitrile and 8% of water in 0.1% formic acid at a flow rate of 500 µl/min for 0.5 min and then 300 µl/min for 2 min. After a liquid-liquid extraction of plasma samples, a step of filtration is performed. This method was validated based on the EMA and French committee of accreditation guidelines. The analysis time is 2.5 min per run, and all analytes eluted within 0.53–1.61 min. The standard curves are linear over the range from 1 to 380 ng/ml for SUNI; from 4.3 to 450 ng/ml for DST-SUNI; from 6 to 1000 ng/ml for PALBO; from 75 to 5000 ng/ml for CABO, from 0.17 to 20 µg/ml for OLA; from 0.35 to 40 µg/ml for SORA and from 1.7 to 200 µg/ml for PAZO. The method also showed satisfactory results in terms precision (below 9.5% for within-run and below 13% for between-run) and accuracy (below 13.5% for within-run and below 14% for between-run). After sampling, all the compounds are stable in whole blood at ambient temperature at least for 6 h and plasma are stable for 48 h at ambient temperature or 4 °C. The method presented here allows to measure the concentrations of 7 targeted therapies in a routine setting. We moreover present here a method that is, to our knowledge, one of the first detailed method aimed at the measurement of palbociclib in human plasma in a routine setting, together with data useful for the management of samples in routine hospital practice[16].

A new liquid chromatography–tandem mass spectrometry (LC–MS/MS) method, performed by electrospray ionization in positive mode using a triple quadrupole mass spectrometry, has been developed and validated for the simultaneous determination of bortezomib (BORT), dasatinib(DASA), imatinib (IMAT), nilotinib (NILO), erlotinib (ERLO), lapatinib (LAPA), sorafenib (SORA), sunitinib (SUNI) and vandetanib (VAND) in human plasma. Separation is achieved on an Hypersil Gold® PFP column using a gradient elution of 10 mM ammonium formate containing 0.1% formic acid (A) and acetonitrile containing 0.1% formic acid (B) at a flow rate of 0.3 mL/min. After addition of the internal standard and protein precipitation, the supernatant is diluted 2-fold in a mixture A and B (50/50, v/v). Two selected reaction monitoring transitions are used for each analyte: one is used for quantitation, the second one is used for confirmation. The standard curves are ranged from 2 ng/mL to 250 ng/mL for BORT, DASA and SUNI and from 50 ng/mL to 3500 ng/mL for the others and were fitted to a 1/x weighted linear regression model. The lowest limits of quantification were 2 ng/mL for BORT, DASA and SUNI and 50 ng/mL for the other TKIs. The method also showed satisfactory results in terms of sensitivity, specificity, precision (intra- and inter-day RSD from 3.7% to 13.8%), accuracy (from 86.8% to 113.5%), recovery as well as stability of the analytes under various conditions. The method also may contribute to better understand the relationship between pharmacokinetics and pharmacodynamics of TKIs in hematological malignancies and solid tumors[17].

A liquid chromatography-tandem mass spectrometry (LC–MS/MS) method was developed and validated for the simultaneous quantification of sorafenib (SORA), its N-oxide active metabolite and of regorafenib (REGO) and its two active metabolites regorafenib N-oxide and N-desmethyl regorafenib N-oxide in hepatocellular carcinoma patients' plasma.A proper analytes' separation was obtained with Synergi Fusion RP column (4 µm, 80 Å, 50 × 2.0 mm) using a gradient elution of 10 mM ammonium acetate with 0.1% formic acid (mobile phase A) and methanol:isopropanol (90:10, v/v, mobile phase B) containing 0.1% formic acid. The analysis was then performed by electrospray ionization in negative mode coupled with a triple quadrupole mass spectrometry, API 4000QT, monitoring two transitions for each analyte, one for the quantification and the other for confirmation. The method could be easily applied to the clinical practice thanks to the short run (7 min), the low amount of patient plasma necessary for the analysis (5 µL) and the fast sample processing based on protein precipitation. The method was therefore fully validated according to FDA and EMA guidelines. The linearity was assessed (R2≥0.998) over the concentration ranges of 50–8000 ng/mL for SORA and REGO, and 30–4000 ng/mL for their metabolites, that appropriately cover the therapeutic plasma concentrations. The presented method also showed adequate results in terms of intra- and inter-day accuracy and precision (CV ≤ 7.2% and accuracy between 89.4% and 108.8%), recovery (≥85.5%), sensitivity, analytes stability under various conditions and the absence of the matrix effect.Once the validation was successfully completed, the method was applied to perform the Cmin quantification of SORA, REGO and their metabolites in 54 plasma samples collected from patients enrolled in a clinical study ongoing at the National Cancer Institute of Aviano[18].

A rapid, sensitive and specific method was developed and validated using LC/MS/MS for determination of sorafenib in human plasma. Sample preparation involved a single protein precipitation step by the addition of 0.1 mL of plasma with 0.5 mL acetonitrile. Analysis of the compounds of interest including the internal standard ([2H3 15N] sorafenib) was achieved on a Waters X-Terra™ C18 (150 mm × 2.1 mm i.d., 3.5 µm) analytical column using a mobile phase consisting of acetonitrile/10 mM ammonium acetate (65:35, v/v) containing 0.1% formic acid and isocratic flow at 0.2 mL/min for 6 min. The analytes were monitored by tandem mass spectrometry with electrospray positive ionization. Linear calibration curves were generated over the range of 7.3–7260 ng/mL for the human plasma samples with values for the coefficient of determination of >0.96. The values for both within day and between day precision and accuracy were well within the generally accepted criteria for analytical methods (<15%)[19].

3. UV Estimation combined with HPLC

A simple, economical, fast, and sensitive RP-HPLC-UV method has been developed for the simultaneous quantification of Sorafenib and paclitaxel in biological samples and formulations using piroxicam as an internal standard. The experimental conditions were optimized and method was validated according to the standard guidelines. The separation of both the analytes and internal standard was achieved on Discovery HS C18 column (250 mm ÿ 4.6 mm, 5 µm) using Acetonitrile and TFA (0.025%) in the ratio of (65:35 V/V) as the mobile phase in isocratic mode at a flow rate of 1 ml/min, with a wavelength of 245 nm and at a column oven temperature of 25 °C in a short run time of 12 min. The limits of detection (LLOD) were 5 and 10 ng/ml while the limits of quantification (LLOQ) were 10 and 15 ng/ml for sorafenib and paclitaxel, respectively. Sorafenib, paclitaxel and piroxicam (IS) were extracted from biological samples by applying acetonitrile as a precipitating and extraction solvent. The method is linear in the range of 15-20,000 ng/ml for paclitaxel and 10-5000 ng/ml for sorafenib, respectively. The method is sensitive and reliable by considering both of its intra-day and inter-day co-efficient of variance. The method was successfully applied for the quantification of the above mentioned drugs in plasma. The developed method will be applied towards sorafenib and paclitaxel pharmacokinetics studies in animal models[20].

Sorafenib, a new oral multikinase inhibitor with antiangiogenic properties, has demonstrated preclinical and clinical activity against several tumor types. The aims of this study were to validate a method for the measurement of sorafenib in plasma from cancer patients, then to test this method in clinical practice. Following liquid–liquid extraction, the compounds were separated with gradient elution (on a C18 ultra sphere ODS column using a mobile phase of acetonitrile/20 mM ammonium acetate), then detected at 255 nm. The calibration was linear in the range 0.5–20 mg/L. Intra- and inter-assay precision was lower than 7 and 10%, respectively, at 0.5, 3 and 20 mg/L. Plasma sorafenib concentrations were measured in 22 cancer patients (99 samples). The mean trough sorafenib concentration (Cmin) and concentration at peak were 4.3 ± 2.5 mg/L (n = 68, CV = 57.5%) and 6.2 ± 3.0 mg/L (n = 31, CV = 47.5%), respectively. Mean sorafenib Cmin in eight patients who experienced grade 3 drug-related adverse events was approximately 1.5-fold greater than that observed in the remaining patients (7.7 ± 3.6 mg/L vs. 4.4 ± 2.4 mg/L, P = 0.0083). In conclusion, the method was successfully used in routine practice to monitor plasma concentrations of sorafenib in cancer patients. Finally, large interindividual variability and higher exposure in patients experiencing severe toxicity support the need for therapeutic drug monitoring to ensure an optimal exposure to sorafenib[21].

Several factors such as low therapeutic index, large interindividual variability in systemic exposure, and the relationships between exposure and toxicity for sorafenib could justify its therapeutic drug monitoring (TDM). To support TDM, a selective and precise high-performance liquid chromatography with ultraviolet detection (HPLC-UV) method was developed and validated for the determination of sorafenib in human plasma.After protein precipitation with acetonitrile, sorafenib and lapatinib (internal standard) were separated using isocratic elution on a Kromasil C18 column using a mobile phase of acetonitrile and 20 mmol/L ammonium acetate in a proportion 53:47 (vol/vol) pumped at a constant flow rate of 1.2 mL/min. Quantification was performed at 260 nm. Validation experiments were carried out after the guidelines for Bioanalytical Method Validation published by the Food and Drug Administration and the European Medicines Agency.Calibration curves were linear over the range 0.1-20 mcg/mL. Inter- and intra-day coefficients of variation were <3%. The limit of detection and the lower limit of quantification were 0.06 and 0.1 mcg/mL, respectively. Recoveries of sorafenib from plasma were >99% in all cases.This method was successfully applied to the determination of the drug in the plasma of 2 patients with cancer receiving sorafenib 200 and 400 mg orally twice daily, respectively, and could be useful for TDM of sorafenib in routine clinical practice[22].

Sorafenib, a new oral multikinase inhibitor with antiangiogenic properties, has demonstrated preclinical and clinical activity against several tumor types. The aims of this study were to validate a method for the measurement of sorafenib in plasma from cancer patients, then to test this method in clinical practice. Following liquid-liquid extraction, the compounds were separated with gradient elution (on a C18 ultrasphere ODS column using a mobile phase of acetonitrile/20 mM ammonium acetate), then detected at 255 nm. The calibration was linear in the range 0.5-20 mg/L. Intra- and inter-assay precision was lower than 7 and 10%, respectively, at 0.5, 3 and 20 mg/L. Plasma sorafenib concentrations were measured in 22 cancer patients (99 samples). The mean trough sorafenib concentration (C(min)) and concentration at peak were 4.3+/-2.5 mg/L (n=68, CV=57.5%) and 6.2+/-3.0 mg/L (n=31, CV=47.5%), respectively. Mean sorafenib C(min) in eight patients who experienced grade 3 drug-related adverse events was approximately 1.5-fold greater than that observed in the remaining patients (7.7+/-3.6 mg/L vs. 4.4+/-2.4 mg/L, P=0.0083). In conclusion, the method was successfully used in routine practice to monitor plasma concentrations of sorafenib in cancer patients. Finally, large interindividual variability and higher exposure in patients experiencing severe toxicity support the need for therapeutic drug monitoring to ensure an optimal exposure to sorafenib[23].

Two simple, rapid, accurate, sensitive and precise spectrophotometric methods (A and B) in ultra violet region have been developed for determination of sorafenib in pure and tablet dosage form. In method A, sorafenib exhibited maximum absorbance at 265 nm with apparent molar absorptivity of 5.2539× 104 in acetonitrile. In method B sorafenib exhibited maximum absorbance at 271 nm with apparent molar absorptivity of 5.0216 × 104 in dimethyl sulfoxide (DMSO). Beer's law was found to be obeyed in the concentration range 2-10 µg/ml in both methods. Correlation coefficient was found to be 0.999 for both methods. The developed method was validated respect to linearity, precision, accuracy. The proposed methods are useful for the routine estimation of sorafenib in pure and tablet dosage form[24].

The solubility of sorafenib free base (SFB) and sorafenib tosylate (ST) in five monosolvents and binary solvents of 2-propanol + 1,4-dioxane was measured over the temperature ranged from 283.15 to 333.15 K by using a UV spectroscopy method. The solubility of SFB and ST in different monosolvents increases with increasing temperature, while in the binary solvents, the solubility shows the maximum value at 0.50 and 0.75 2-propanol mole fraction for SFB and ST, respectively. The Apelblat model and the CNIBS/R-K model were applied to correlate the solubility data, which shows that the two selected thermodynamic models could give satisfactory results. Moreover, mixing thermodynamic properties of enthalpy, entropy, and Gibbs free energy of SFB and ST were obtained based on the nonrandom two-liquid model for further understanding of the mixing behavior[25].

A simple, economical, fast, and sensitive RP-HPLC-UV method has been developed for the simultaneous quantification of Sorafenib and Paclitaxel in biological samples and formulations using piroxicam as an internal standard.First method which simultaneously determines the Sorafenib and Paclitaxel in nano-pharmaceutical formulations and plasma with simple mobile phase composition and shorter analysis time. The method was successfully applied for the in-vitro studies of Sorafenib and Paclitaxel nanosuspension formulations and pharmacokinetics studies in animal model. The experimental conditions were optimized and method was validated according to the standard guidelines. The separation of both the analytes and internal standard was achieved on Discovery HS C18 column (250 mm ÿ 4.6 mm, 5 µm) using Acetonitrile and TFA (0.025%) in the ratio of (65:35 V/V) as the mobile phase in isocratic mode at a flow rate of 1 ml/min, with a wavelength of 245 nm and at a column oven temperature of 25 °C in a short run time of 12 min. The limits of detection (LLOD) were 5 and 10 ng/ml while the limits of quantification (LLOQ) were 10 and 15 ng/ml for sorafenib and paclitaxel, respectively. Sorafenib, paclitaxel and piroxicam (IS) were extracted from biological samples by applying acetonitrile as a precipitating and extraction solvent. The method is linear in the range of 15-20,000 ng/ml for paclitaxel and 10-5000 ng/ml for sorafenib, respectively. The method is sensitive and reliable by considering both of its intra-day and inter-day co-efficient of variance. The method was successfully applied for the quantification of the above mentioned drugs in plasma. The developed method will be applied towards sorafenib and paclitaxel pharmacokinetics studies in animal models[26].

3.1. Voltametric method

Adsorptive stripping differential pulse voltammetry (AdSDPV) was applied to the assay of sorafenib in human serum sample. Cyclic voltammetry at a carbon based screen printed electrode (SPE) permitted to detect the irreversible oxidation of SOR with formation of a new compound reversibly oxidized at a lower potential. Quantitative assays were realized using a chitosan/carboxylic acid functionalized multiwalled carbon nanotube modified glassy carbon electrode in 0.1 M phosphate buffer pH 7.0 in the presence of 50 % methanol. The AdSDPV method provided two linear responses within the concentration ranges 1×10−8–8×10−8 M and 1×10−7–8×10−7 M in serum with LOQ and LOD of 3.2×10−9 and 9.6×10−10 of lower linear range, respectively. The recovery of sorafenib in spiked serum was 97.5 %[27].

3.2. Spectroscopic method

Six sequential spectrophotometric-based univariate methods were developed and validated for the simultaneous estimation of three novel anticancer drugs vandetanib (VAN), dasatinib (DAS), and sorafenib (SOR) in a mixture, without the requirement for separation. These methods are novel, simple, precise, and accurate. Different steps including zero crossing, ratio-based, and/or derivative spectra were utilized to develop these analytical methods, namely, ratio difference spectrophotometric method, constant center method, successive derivative ratio method, isoabsorptive method, mean centering of the ratio spectra method, and derivative ratio spectrum–zero crossing method. The calibration curve linearity was ranged from 2 to 9, 2–9, and 3–9 µgmL−1 for VAN, DAS, and SOR, respectively. These established methods were applied for the quantification of the three selected drugs in different biological fluids (spiked human plasma and urine) and pharmaceutical preparations. The aforementioned methods were established for the concurrent estimation of ternary and binary mixtures to enhance the signal-to-noise ratio. The results did not statistically differ from the other reported methods, indicating no significant difference in accuracy and precision at p = 0.05[28].

Two simple, sensitive, and specific spectrophotometric methods were developed and validated for the estimation of sorafenib in pure and its dosage form. The proposed method A was based on the interaction of the drug with 2, 4-dinitrophenylhydrazine in the presence of an acid catalyst, followed by treatment with a methanolic potassium hydroxide; an intensely colored chromogen was formed that was measured in dimethyl formamide as the diluting solvent at 540 nm. Method B was based on reaction with ninhydrin in basic medium form colored product having absoption maximum at 495 nm. Beer's law was obeyed in the concentration ranges of 2-10 µg/ml and 5-30 µg/ml for method A and B respectively, with good correlation coefficient of 0.999 for both methods. The proposed methods were applied successfully for the estimation of sorafenib in pure form and in pharmaceutical preparation without interference from commonly used additives[29].

4. Conclusion

Here we summarised all the various analytical methods for the estimation of Sorafenib which is an anticancer agent. The drug can be estimated by using HPLC method, Voltametric method, LC-MS and UV method in single as well as in combined dosage form. This collection may be use full for rapid glance of various analytical methods for estimation of Sorafenib.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

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