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Overall Review on Analytical Method Development and Validation of Sunitinib

Ramanjaneyulu Seemaladinne

Department of Pharmacy, Lamar university 4400 S M L King Jr Pkwy, Beaumont, TX 77705

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***Corresponding Author**
Ramanjaneyulu Seemaladinne

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Abstract

In this review article determines the different analytical methods for the quantitative establishment of Sunitinib by using HPLC, HPLCMS, HPLC-UV, LC-MS/MS. Pharmaceutical analytical method development of Sunitinib requires valid analytical procedures for quantitative and qualitative analysis in Pharmaceuticals dosage formulations and human serum. This assessment explains that the superiority of the HPLC/LC-MS methods reviewed is based on the quantitative analysis of drugs in formulations, (API), biological fluids such as serum and plasma.

Introduction

Sunitinib, sold under the brand name Sutent, is a medication used to treat cancer [2]. It is a small-molecule, multi-targeted receptor tyrosine kinase (RTK) inhibitor that was approved by the FDA for the treatment of renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumor (GIST) on January 26, 2006. Sunitinib was the first cancer drug simultaneously approved for two different indications. [3] As of August 2021, Sunitinib is available as a generic medicine in the US [4].

Mechanism of action

Sunitinib inhibits cellular signalling by targeting multiple receptor tyrosine kinases (RTKs). These include all receptors for platelet-derived growth factor (PDGF-Rs) and vascular endothelial growth factor receptors (VEGFRs), which play a role in both tumor angiogenesis and tumor cell proliferation. The simultaneous inhibition of these targets therefore reduces tumor vascularization and triggers cancer cell apoptosis and thus results in tumor shrinkage.

Sunitinib also inhibits CD117 (c-KIT), [13] the receptor tyrosine kinase that (when improperly activated by mutation) drives the majority of gastrointestinal stromal cell tumors [14]. It has been recommended as a second-line therapy for patients whose tumors develop mutations in c-KIT that make them resistant to imatinib, or who they cannot tolerate the drug [15] [16].

In addition, Sunitinib binds other receptors [2]. These include:

1. RET
2. CD114
3. CD135

The fact that Sunitinib targets many different receptors, leads to many of its side effects such as the classic hand-foot syndrome, stomatitis, and other dermatologic toxicities.

Medical uses

Gastrointestinal stromal tumor

Like RCC, GIST does not generally respond to standard chemotherapy or radiation. Imatinib was the first cancer agent proven effective for metastatic GIST and represented a major development in the treatment of this rare but challenging disease. However, approximately 20% of patients do not respond to imatinib (early or primary resistance), and among those who do respond initially, 50% develop secondary imatinib resistance and disease progression within two years. Prior to Sunitinib, patients had no therapeutic option once they became resistant to imatinib.

Sunitinib offers patients with imatinib-resistant GIST a new treatment option to stop further disease progression and, in some cases, even reverse it. This was shown in a large, Phase III clinical trial in which patients who failed imatinib therapy (due to primary resistance, secondary

resistance, or intolerance) were treated in a randomized and blinded fashion with either Sunitinib or placebo.

The study was unblinded early, at the very first interim analysis, due to the clearly emerging benefit of Sunitinib. At that time, patients receiving placebo were offered to switch over to Sunitinib. In the primary endpoint of this study, median time to tumor progression (TTP) was more than four-fold longer with Sunitinib (27 weeks) compared with placebo (six weeks, P<.0001). These are based on the assessments of an independent radiology lab assessment. The benefit of Sunitinib remained statistically significant when stratified for a multitude of prespecified baseline factors.

Among the secondary endpoints, the difference in progression-free survival (PFS) was similar to that in TTP (24 weeks' vs six weeks, P<.0001). Seven percent of Sunitinib patients had significant tumor shrinkage (objective response) compared with 0% of placebo patients (P=.006). Another 58% of Sunitinib patients had disease stabilization vs. 48% of patients receiving placebo. The median time to response with Sunitinib was 10.4 weeks [5]. Sunitinib reduced the relative risk of disease progression or death by 67%, and the risk of death alone by 51%. The difference in survival benefit may be diluted because placebo patients crossed over to Sunitinib upon disease progression, and most of these patients subsequently responded to Sunitinib.

Sunitinib was relatively well tolerated. About 83% of Sunitinib patients experienced a treatment-related adverse event of any severity, as did 59% of patients who received placebo. Serious adverse events were reported in 20% of Sunitinib patients and 5% of placebo patients. Adverse events were generally moderate and easily managed by dose reduction, dose interruption, or other treatment. Nine percent of Sunitinib patients and 8% of placebo patients discontinued therapy due to an adverse event.

Fatigue is the adverse event most commonly associated with Sunitinib therapy. In this study, 34% of Sunitinib patients reported any grade of fatigue, compared with 22% for placebo. The incidence of grade 3 (severe) fatigue was similar between the two groups, and no grade 4 fatigue was reported.

Meningioma

Sunitinib is being studied for treatment of meningioma which is associated with neurofibromatosis.

Pancreatic neuroendocrine tumors

In November 2010, Sutent gained approval from the European Commission for the treatment of 'unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumors with disease progression in adults'. In May 2011, the USFDA approved Sunitinib for treating patients with 'progressive neuroendocrine cancerous tumors located in the pancreas that cannot be removed by surgery or that have spread to other parts of the body (metastatic)'

Renal cell carcinoma

Sunitinib is approved for treatment of metastatic RCC. Other therapeutic options in this setting are pazopanib (Votrient), sorafenib (Nexavar), temsirolimus (Torisel), interleukin-2 (Proleukin), everolimus (Afinitor), bevacizumab (Avastin), and aldesleukin.

RCC is generally resistant to chemotherapy or radiation. Prior to RTKs, metastatic disease could only be treated with the cytokines interferon alpha (IFNα) or interleukin-2. However, these agents demonstrated low rates of efficacy (5%-20%).

In a phase III study, median progression-free survival was significantly longer in the Sunitinib group (11 months) than in the IFNα group (five months), a hazard ratio of 0.42. In the secondary endpoints, 28% had significant tumor shrinkage with Sunitinib compared to 5% with IFNα. Patients receiving Sunitinib had a better quality of life than IFNα. An update in 2008 showed that the primary endpoint of median progression-free survival (PFS) remained superior with Sunitinib: 11 months versus 5 months for IFNα, P<.000001. Objective response rate also remained superior: 39-47% for Sunitinib versus 8-12% with IFNα, P<.000001

Sunitinib treatment trended towards a slightly longer overall survival, although this was not statistically significant.

Median overall survivability was 26 months with Sunitinib vs 22 months for IFNα regardless of stratification (P-value ranges from .051 to .0132, depending on statistical analysis).

The first analysis includes 25 patients initially randomized to IFNα who crossed over to Sunitinib therapy, which may have confounded the results; in an exploratory analysis that excluded these patients, the difference becomes more robust: 26 vs 20 months, P=.0081.

Patients in the study were allowed to receive other therapies once they had progressed on their study treatment. For a "pure" analysis of the difference between the two agents, an analysis was done using only patients who did not receive any post-study treatment. This analysis demonstrated the greatest advantage for Sunitinib: 28 months' vs 14 months for IFNα, P=.0033. The number of patients in this analysis was small and this does not reflect actual clinical practice and is therefore not meaningful.

Hypertension (HTN) was found to be a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with Sunitinib.[12] Patients with mRCC and Sunitinib-induced hypertension had better outcomes than those without treatment-induced HTN (objective response rate: 54.8% vs 8.7%; median PFS: 12.5 months, 95% confidence interval [CI] = 10.9 to 13.7 vs 2.5 months, 95% CI = 2.3 to 3.8 months; and OS: 30.9 months, 95% CI = 27.9 to 33.7 vs 7.2 months, 95% CI = 5.6 to 10.7 months; P < .001 for all).

Literature Review

Kavitha J, et al**.** developed and validated simple zero (D0), first (D1) and second (D2) order derivative UV

spectrophotometric methods for the determination of Sunitinib malate in pharmaceutical dosage form. It was solubilised in distilled water and the resultant solution adsorption maximum (λ max) was at 431, 457, and 489 nm in D0, D1 and D2 order derivative modes respectively. The developed method was validated as per ICH guidelines. Linearity was obtained over the concentration range of 2-12 µg/ ml in all the derivative modes. Limit of detection (LOD) was found to be 0.291,0.324,0.993µg/ml and Limit of quantification (LOQ) was found to be 0.883, 0.324,0.993µg/ml for D0, D1 and D2 order derivative modes respectively. The proposed method demonstrated an excellent intra-day precision and inter-day precision. Mean recovery was found within the range of 98.19 – 98.62%. [25]

Amena Tazeen, et al. developed and validated a simple and sensitive spectroscopic method in UV-visible region for the determination of Sunitinib malate in bulk and formulation. A method was performed with methanol which shows maximum absorbance at 432 nm. The correlation coefficient was found to be R 2 = 0.999. The proposed method has been successfully applied for the assay of the drug in pharmaceutical formulations. No interference was observing during the method development and validation of the drug. [26]

Mohsen padervand, et al. (2017) developed and validated chial HPLC method for Sunitinib malate. Since Sunitinib malate shows Z-E isomerism, various reverse phase high performance liquid chromatography (RP-HPLC) programs were designed to access quantitative determination and good separation of Z-E stereoisomers. Moreover, some impurities including N-oxide and impurity B were separated from the main isomer with acceptable resolution The opted conditions for quantitative analysis were C8-Hector column as stationary phase, methanol as solvent, ammonium acetate buffer containing trimethylamine as mobile phase, the pH of mobile phase of 8.5, the flow rate of 1.0 mL/min, and detection at 425 nm. In this situation the peaks of E and Z isomers were at 16.3 and 19.7 min. Full validation of the designed method was done based on ICH guidelines. [27]

Benoit blanchet, et al. developed a simple and sensitive high-performance liquid chromatographic method with UV-Visible detection for quantification of Sunitinib concentrations in human plasma. After a liquid–liquid extraction with ethyl acetate, Sunitiniband ranitidine (internal standard) are separated on cyanopropyl column using a simple binary mobile phase of ammonium acetate buffer (20 mM; pH 6.8): acetonitrile (55:45, v/v). Samples were eluted isocratically at a flow rate of 1 mL/min throughout the 10 min run. Dual wavelength mode was used, with ranitidine monitored at 255 nm, and Sunitinib at 431 nm. The calibration was linear in the range 20–200 ng/mL. Inter- and intra-day coefficients of variation were less than 7%. This method is sensitive, accurate and selective.

Marie Christine Etienne - grimaldi et al. developed and validated simple, high-performance liquid chromatography (HPLC) method for assay with UV detection. A stability study of Sunitinib and SU12662 in different light exposure conditions was done. Due to photo-instability of the compounds, blood sampling and the whole handling procedure have to be performed quickly and with minimal light exposure (6–7 lx). Following single organic extraction with tert-butyl methyl ether, HPLC analysis was performed on an ODS column and UV detection was monitored at 369 nm (run time 15 min). The method was selective and sensitive enough (limit of detection approximately 1 ng/ml) to quantify minimal concentrations at steady state (Css min) of Sunitinib and SU12662 in treated patients.

Murari gurjar, et al. (2020) developed a sensitive HPLC method for the quantitation of Sunitinib (SU) and its active metabolite N-desethyl-Sunitinib (SU12662) in human plasma. The analytes were extracted from 500 µl of plasma using liquid–liquid extraction followed by protein precipitation. Chromatographic separation of two analytes and internal standard, vandetenib, was achieved on a hydrophilic interaction liquid chromatography analytical column using a gradient program. Calibration curves were linear over the range of 10–250 ng/ml for both SU and SU12662. The method was validated according to the US FDA guidelines for bioanalytical methods. Accuracy of the method at 10 ng/ml for SU and SU12662 was 8.7 and 6.7%, respectively, and precision was 10.18% and 17.3%, respectively. The method was specific, sensitive determination of SU and SU12662 in human plasma in a single analytical run which makes it useful for therapeutic drug monitoring.

Patton minkin et al. (2008) developed a rapid, sensitive method by using LC/MS/MS for determination of Sunitinib in human plasma. Sample preparation involved a liquid–liquid extraction by the addition of 0.2 mL of plasma with 4.0 mL tert-butyl-methyl-ether extraction solution containing 25 ng/mL of the internal standard clozapine. Separation of compounds was achieved on a C18 (50 mm × 2.1 mm i.d., 3.5 µm) analytical column using a mobile phase consisting of acetonitrile/H20 (65:35, v/v) containing 0.1% formic acid and isocraticflow at 0.150 mL/min for 3 min. The analytes were monitored by tandem-mass spectrometry with electrospray positive ionization. Linear calibration curves in human plasma were generated over the range of 0.2–500 ng/mL with values for the coefficient of determination of >0.9950. Within- and between day precision and accuracy were ≤10%. The method was applied to the quantitation of Sunitinib in plasma samples from a patient receiving daily oral therapy with Sunitinib.

Jacek musijowski, et al. developed an original method based on liquid chromatography with single quadrupole electrospray ionization mass spectrometry for the determination of Sunitinib in human plasma. The quantitation limit of the method at 0.10 ng/mL is

comparable to that of tandem mass spectrometry assays. Liquid–liquid extraction with a mixture of n-hexane/isopropanol (90:10 v/v) allowed recoveries at the level of 70%. Measurements were performed using a Zorbax SB-C-18 column (3.0 mm × 150 mm, 3.5 µm) and isocratic elution with (A) 0.1% aqueous formic acid and (B) acetonitrile/methanol (80:20 v/v) in an A/B ratio of 55:45 at 35°C. Under these conditions, Sunitinib is eluted at 3.8 min in 6 min of the total run time. The linearity of the calibration curve ranges from 0.10 to 150 ng/mL. The baseline separation of Sunitinib and its primary metabolite, N-des-ethyl Sunitinib (SU12662), as well as sharp peak shapes, suggest a possibility of extending the applied methodology to the quantitative determination of both compounds. Isotopically labeled Sunitinib was used as the internal standard. All required validation tests met the acceptance criteria and proved the method's reliability and robustness. The method may be conveniently applied to study the pharmacokinetics of Sunitinib in humans.

Qingyuzhou, et **al.**developed and validated a liquid chromatography–tandem mass spectrometry (LC–MS/MS)-based method combined with protein precipitation, liquid–liquid extraction and solid-phase extraction techniques for the determination of Sunitinib in mouse plasma, brain tumor and normal brain tissue, respectively. The instrument was operated under the multiple reaction monitoring (MRM) mode using electrospray ionization (ESI) in the positive ion mode. A good linear relationship with coefficients of determination ≥0.99 was achieved over the concentration ranges of 1.37–1000 ng/mL for plasma and 4.12–1000 ng/g for the normal brain and brain tumor. The limits of quantification (LOQs) for Sunitinib in mouse plasma, brain tumor and normal brain tissue are 1.37 ng/mL, 4.12 ng/g and 4.12 ng/g, respectively. The reproducibility of the LC–MS/MS method is reliable, with the intraand inter-day precision being less than 15% and accuracy within ±15%. The establishedmethod was successfully applied to the characterization of Sunitinib disposition in the brain and brain tumor as well as its systemic pharmacokinetics in a murine orthotopic glioma model.

Peter debruijn et al. developed and validated a rapid and sensitive Ultra performance liquid chromatography/tandem mass spectrometry (UHPLC–MS/MS) method for the quantitative determination of Sunitinib and its n-desethyl metabolite SU12662, in 100 µL aliquots of human potassium EDTA plasma with deuterated Sunitinib as internal standard. The extraction involved a simple liquid–liquid extraction with tert-butyl methyl ether. Chromatographic separations were achieved on an Acquity UHPLC® BEH C18 1.7 µm, 2.1 mm × 50 mm column eluted at a flow rate of 0.250 ml/min on a gradient of acetonitrile. The overall cycle time of the method was 4 min, with elution times of 1.05, 1.43, 0.95, and 1.34 min, for the E (trans)- and Z (cis)-isomers of Sunitinib and the E (trans)- and Z (cis)-isomers of SU12662, respectively. The multiple reaction monitoring transitions were set at 399 > 326 (m/z), at 371 > 283 (m/z) and at 409 > 326 (m/z) for Sunitinib, SU12662 and the internal standard, respectively. The calibration curves were linear over the range of 0.200 to 50.0 ng/ml with the lower limit of quantitation validated at 0.200 ng/ml for both Sunitinib and SU12662. The within-run and between-run precisions were within 11.7%, while the accuracy ranged from 90.5 to 106.8%.

Michael rodamer et al. developed and validated a sensitive, precise and accurate quantitative liquid chromatography/tandem mass spectrometry (LC–MS/MS) method for the measurement of Sunitinib (SU11248) and N-desethyl Sunitinib (SU12662) in human plasma. All sample handling was done under strict light protection. The sample preparation method employed acetonitrile protein precipitation using d5-SU11248 as an internal standard. The processed samples were chromatographed on a polymeric reversed-phase analytical column and analyzed by triple-quadrupole MS/MS in multiple reaction monitoring (MRM) mode using positive Turboionspray (TISP). The LC–MS/MS method described in this paper presents high absolute recovery (86.2% SU11248, 84.8% SU12662), high sensitivity (lower limit of quantitation of 0.06 ng/mL for both analytes), high inter-day precision (1.6–6.1% SU11248, 1.1–5.3% SU12662) and high analytical recovery (99.8–109.1% SU11248, 99.9– 106.2% SU12662), as well as excellent linearity over the concentration range 0.060–100 ng/mL (r2 > 0.999) with a short runtime of only 4.0 min. Results on the stability of SU11248 and SU12662 in human plasma are presented. During validation plasma fromintensive care patients receiving many drugs were tested for interference and incurred samples were analyzed. The method met all criteria of the EMA and FDA guidelines during validation and was successfully applied to a pharmacokinetic study in healthy human volunteers.

Lutz Gotze, et al. developed a simple and rapid quantification method for various TKIs in human plasma. A simultaneous test for six TKIs (Erlotinib, imatinib, lapatinib, nilotinib, sorafenib, Sunitinib) using liquid chromatography tandem mass spectrometry in a multiple reaction monitoring mode. After protein precipitation the specimens were applied to the HPLC system and separated using a gradient of acetonitrile containing 1% formic acid with 10 mM ammoniumformate on an analytic RP-C18 column. The calibration range was 10– 1000 ng/mL for Sunitinib and 50–5000 ng/mL for the other TKIs with coefficients of determination ≥ 0.99 for all analytes. The intra- and inter day coefficients of variation were ≤ 15% and the chromatographic run time was 12 min. Plasma specimens were stable for measurement for at least 1 week at 4 °C.

Irina Andriamanana, et al. developed and validated a new liquid chromatography– tandem mass spectrometry (LC–MS/MS) method by electrospray ionization in positive mode using a triple quadrupole mass spectrometry for the simultaneous determination of bortezomib (BORT),

dasatinib (DASA), imatinib (IMAT), nilotinib (NILO), Erlotinib (ERLO), lapatinib (LAPA), sorafenib (SORA), Sunitinib (SUNI) and vandetenib (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 contributeto better understand the relationship between pharmacokinetics and pharmacodynamics of TKIs in hematological malignancies and solid tumors.

Monireh Hajmalek et al. developed and validated a simple high performance thin layer chromatography (HPTLC)for determination of Sunitinib malate and possible impurities. The samples were applied in forms of bands on an aluminum. TLC plate pre-coated with silica gel and were separated using dichloromethane: methanol: toluene: ammonia solution as the mobile phase. Sunitinib malate was thoroughly separated from impurities including Eisomer, Sunitinib N-oxide and impurity B with a retention factor (RF) of 0.35±0.02. Quantitative analysis of Sunitinib was carried out using a mobile phase consisting of dichloromethane: methanol: ammonia solution, RF value was 0.53±0.02 for Z isomer. Detection was performed densitometrically in absorbance mode at 430 nm. This method was found to produce sharp, symmetrical, and well resolved peaks. Linear relationship with the coefficients of determination > 0.99 was achieved over the concentration range of 27.34 to 437.5 ng/spot. This method provides robust, replicable and accurate results with acceptable sensitivity.

Conclusion

A sensitive and accurate RP-HPLC methods, stability-indicating HPLC, HPLC-PDA, HPLC-UV, stability indicating HPTLC and HPLC-MS, was developed for the estimation of Sunitinib, in pharmaceutical dosage forms, human plasma, the above methods was evaluated for Specificity, Linearity, Accuracy, Precision, Ruggedness and Robustness as per ICH&FDA guidelines.

Conflict of Interest

Author are declared No Conflict of Interest

Acknowledgement

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Author Contribution

Author Contributed fully.

Ethical Considerations

Not Applicable

Inform Consent

Not Applicable

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