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Various analytical methods for estimation of Imatinib: A review

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Abstract

Imatinib, is an oral chemotherapy medication used to treat cancer. Specifically, it is used for chronic myelogenous leukemia and acute lymphocytic leukemia that are Philadelphia chromosome-positive, certain types of gastrointestinal stromal tumors, hypereosinophilic syndrome, chronic eosinophilic leukemia, systemic mastocytosis, and myelodysplastic syndrome. There are various analytical methods for estimation of the drug. This paper list outs the various analytical methods for the drug.

Keywords: Imatinib; Anticancer; Analytical methods; Review.

1. Introduction

Imatinib is a benzamide obtained by formal condensation of the carboxy group of 4-[(4- methylpiperazin-1-yl)methyl]benzoic acid with the primary aromatic amino group of 4 methyl-N(3)-[4-(pyridin-3-yl)pyrimidin-2-yl]benzene-1,3-diamine. It's solubility is soluble in water-(200mg/ml), DMSO-(100mg/ml), DMF-(10mg/ml), PBS-(2mg/ml) and Sparingly Soluble in Ethanol (0.2mg/ml). It's pKa value is Strongest acidic (12.69) and strongest basic (7.84).Molecular weight-493.6 g/molestructure of compound.

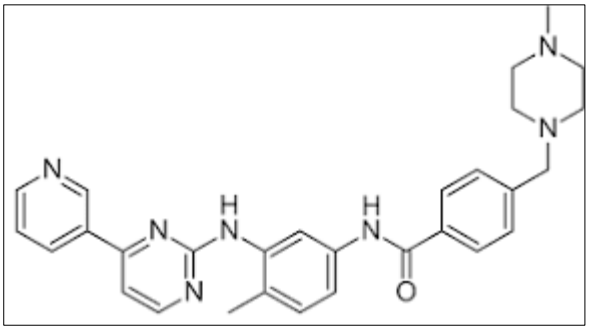

Figure 1 Structure of Imatinib

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2. UPLC Method

This study aimed to develop a rapid, user-friendly, economic and sensitive method for analyzing imatinib mesylate (IMA) and erlotinib hydrocloride (ERLO) in mice plasma using ultrahigh performance liquid chromatography (UPLC). Separation was achieved by isocratic elution using a mobile phase consisting of the mixture of 3mM triethylamine and acetonitrile with the ratio of 60:40 using XTerra® RP8 column (5 µm 4.6x150 mm). The retention time for IMA was 4.9 minutes with a flow rate of 1.5mL/min, while the retention time for ERLO was 5.0 minutes with a flow rate of 0.8mL/min. Injection volume was set to 20µL and the detector wavelength was 320 nm. Detection limits for imatinib mesylate and erlotinib hydrochloride were 95 and 72 ng/mL, respectively. This method was validated in terms of linearity, selectivity, recovery, precision and accuracy. This simple and sensitive method can be successfully used in research and easily adapted for analyses of other types of tyrosine kinases receptor inhibitors[1].

3. LC-MS

The introduction of imatinib, an oral tyrosine kinase inhibitor, as first-line standard therapy in patients with unresectable, metastatic, or recurrent gastro-intestinal stromal tumor (GIST), strongly improved their treatment outcomes. A fast and cheap method was developed and validated using high-performance liquid chromatography-mass spectrometry for quantification of imatinib in human serum and tamsulosin as the internal standard. Remarkable advantages of the method includes use of serum instead of plasma, less time spent on processing and analysis, simpler procedures, and requiring reduced amounts of biological material, solvents, and reagents. LC-MS, HPLC and UV Spectrophotometry validated methods have proved to be linear, accurate, precise, and robust, it is suitable for pharmacokinetic assays, such as bioavailability and bioequivalence, and is being successfully applied in routine therapeutic drug monitoring in the hospital service[2].

Imatinib mesylate has been a breakthrough treatment for chronic myeloid leukemia. It has become the ideal tyrosine kinase inhibitor and the standard treatment for chronic-phase leukemia. Striking results have recently been reported, but intolerance to imatinib and noncompliance with treatment remain to be solved. Molecular monitoring by quantitative real-time polymerase chain reaction is the gold standard for monitoring patients, and imatinib blood levels have also become an important tool for monitoring. A fast and cheap method was developed and validated using high-performance liquid chromatography-mass spectrometry for quantification of imatinib in human serum and tamsulosin as the internal standard. Remarkable advantages of the method includes use of serum instead of plasma, less time spent on processing and analysis, simpler procedures, and requiring reduced amounts of biological material, solvents, and reagents. Stability of the analyte was also studied. This research also intended to drive the validation scheme in clinical centers. The method was validated according to the requirements of the US Food and Drug Administration and Brazilian National Health Surveillance Agency within the range of 0.500–10.0 µg/mL with a limit of detection of 0.155 µg/mL. Stability data for the analyte are also presented. Given that the validated method has proved to be linear, accurate, precise, and robust, it is suitable for pharmacokinetic assays, such as bioavailability and bioequivalence, and is being successfully applied in routine therapeutic drug monitoring in the hospital service[3].

A sensitive and selective liquid chromatographic-tandem mass spectrometric (LC-MS/MS) method was developed and validated for the trace analysis (> 1 ng/mL level) of 2-methyl-5-aminophenyl)-4-(3-pyridyl)-2-pyrimidine (Imp-A) a genotoxic impurity in imatinib mesylate drug substances. LC-MS/MS analysis of Imp-A was done on Inertsil C18 (150 mm × 4.6 mm) 5 µm column and 0.1% formic acid in 1000 mL of water was used as buffer in mobile phase A and acetonitrile in mobile phase B. Gradient program was developed for rapid analysis. The flow rate was 1.0 mL/min and elution was monitored by mass spectrophotometer. The method was validated as per International Conference on Harmonization (ICH) guidelines. LC-MS/MS is able to quantitate up to 1 ng/mL of Imp-A[4].

A reversed-phase selective and sensitive liquid chromatography coupled with tandem mass spectrometric (LC-MS/MS) method was developed and validated for the trace analysis of (0.5 ppm level) of 4-(bromomehtyl)benzoic acid genotoxic impurity in imatinib mesylate drug substance. The method obtained with Inertsil C18 column (250 mm ×4.6 mm, 5.0 µm) with negative electrospray ionization in multiple reaction monitoring (MRM) detection mode. Mobile phase was 0.1% formic acid in water and acetonitrile in the ratio of 35:65(v/v). Isocratic program was developed and the flow rate was 1.0 mL/min and elution was monitored by mass spectrophotometer. The method was validated as per International Conference on Harmonization (ICH) guidelines and was able to quantitate up to 0.5ppm of 4-bromo mehtyl benzoic acid[5].

Analytical methods using high performance liquid chromatography coupled to ultraviolet detection (HPLC-UV) or liquid chromatography tandem mass spectrometry (LC-MS/MS) have been reported for the quantification of oral tyrosine

kinase inhibitors (TKIs) such as imatinib, nilotinib, and dasatinib in biological fluids. An LC-MS/MS method can simultaneously assay multiple TKIs and their metabolites with high sensitivity and selectivity for low plasma concentrations less than 1 ng/mL. For quantification of imatinib, nilotinib, and dasatinib, a limit of quantification (LOQ) of less than 10 ng/mL, 10 ng/mL, and 0.1 ng/mL, respectively, in the clinical setting is necessary. Because simpler and more cost-efficient methodology is desired for clinical analysis, plasma concentrations of imatinib and nilotinib (target trough concentrations of 1000 ng/mL and 800 ng/mL, respectively) could be assayed by an HPLC-UV method after comparison with results obtained from the standard LC-MS/MS method. However, in the quantification of dasatinib, the LC-MS/MS method that has high sensitivity and selectivity and is free from interference by endogenous impurities is superior to the HPLC-UV method. Highly precise analytical methods are needed for individualized treatment via dose adjustment of oral anticancer drugs, in particular those with low target plasma concentrations less than 10 ng/mL[6].

An isocratic online-enrichment HPLC-assay was developed allowing for the simple and fast separation and quantitation of STI-571 and its main metabolite N-desmethyl-STI (N-DesM-STI) in plasma, urine, cerebrospinal fluid (CSF), culture media, and cell preparations in various concentrations using UV-detection at 260 nm. The analytical procedure consists of an online concentration of STI-571 and N-DesM-STI in the HPLC system followed by the elution on a ZirChrom-PBD analytical column. Time of analysis is 40 min including the enrichment time of 5 min. The detection limit is 10 ng/mL in plasma, CSF, culture medium (RPMI), and 25 ng/mL in urine for both STI-571 and N- DesM-STI. The intra-day precision, as expressed by the coefficient of variation (CV), in plasma samples ranges between 1.74 and 8.60% for STI-571 and 1.45 and 8.87% for N- DesM-STI. The corresponding values for urine measurements are 2.17–7.54% (STI-571) and 1.31–9.51% (N-DesM-STI). The inter-day precision analyzed over a 7-month time period was 8.31% (STI-571) or 6.88% (N-DesM-STI) and 16.45% (STI-571) or 14.83% (N-DesM-STI) for a concentration of 1000 ng/mL in plasma and 750 ng/mL in urine, respectively. Moreover, we demonstrate that with an alternative, but more time and labor consuming sample preparation and the implementation of electrochemical detection, a detection limit <10 ng/mL can be achieved. The method described was used to perform pharmacokinetic measurements of STI-571 and N-desmethyl-STI in patient samples and for kinetic measurements of intracellular STI-571 and N-DesM-STI following *in vitro* incubation[7].

4. HPLC Methods

A study was conducted on Relative Response Factor by changing the High Performance Liquid Chromatography (HPLC) chromatographic method conditions like different HPLC columns, Flow rate, pH, Temperature, Buffer concentration, Detector wavelength, different Detectors (Ultraviolet & Photo Diode Array Detectors) and different Solvent grades and observed the variations in established RRF. The authors have studied the impact on RRF by changing the Robustness parameters and HPLC columns and all the results were compared. The comparision study has shown that any slight variations in method conditions, the impact is observed on established RRF values[8].

A sensitive, robust and selective stability indicating RP-HPLC method for the related substances determination of process impurities and their degradation products of Imatinib in tablet dosage form was developed and validated. Stability indicating power of the method was established by forced degradation experiments and mass balance study. The chromatographic separation was performed on Symmetry C18 (150 mm, 4.6 mm) 5m make: Waters column, using gradient elution of mobile phase-A (prepare a mixture of 500 volumes of pH 3.0 buffer solution and 500 volumes of methanol) and mobile phase-B (prepare a mixture of 40 volumes of pH 3.0 buffer solution and 960 volumes of methanol) at a flow rate of 1.0 ml/minute. The buffer solution was prepared by dissolving 7.5 g of 1-octane sulfonic acid sodium salt in water and adjusting the pH to 3.0 with ortho-phosphoric acid. The column oven temperature and sample temperature was maintained at 27°C and ambient respectively. Detection was performed at 240 nm. The injection volume was set to 20µl and the run time of this method is 65 minutes. The retention time of the Imatinib peak was found to be about 21 minute. The method was further evaluated for its stability indicating capability by acid hydrolysis, alkali hydrolysis, water hydrolysis, oxidation degradation, thermal degradation and photolytic degradation. All acceptance criteria of International Conference on Harmonization guideline for validation were covered in method validation. This method can be used for quality control sample during manufacture and during stability sample analysis[9].

A gradient reversed-phase HPLC method with PDA detector has been developed for the purity evaluation of Imatinib Mesylate in bulk drug. The impurities are (2-methyl-5-aminophenyl)-4-(3-pyridyl)-2- pyrimidine amine (i.e. Imp-A) and N-[4-methyl-3-(4-methyl-3-yl-pyrimidin-2-ylamino)-phenyl]-4-chloromethyl benzamide (i.e. Imp-B). The analysis was performed using inertsil ODS 3V column (150 × 4.6 mm, 5µ) as a stationary phase with column oven temperature 35°C and UV detection at 268 nm. The separation was achieved using gradient program of buffer (A Buffer used was of 0.1% Triethyl amine in water and pH adjusted to 2.9 with glacial acetic acid) and mixture of methanol and Acetonitrile. The method was optimized based on the peak shapes and resolution of Imp-A and Imp-B. The method was validated as per International Conference of Harmonization (ICH) guidelines in terms of limit of detection (LOD), Limit of quantitation (LOQ), linearity, precision, accuracy, specificity, robustness and solution stability. The LOD and LOQ values were found

to be 0.024 µg/ml and 0.08 µg/ml, respectively. The sample concentration were injected was 10 mg/ml. The method is linear within the range of 0.08-0.3 µg/ml for both the Impurities[10].

A simple, sensitive, isocratic and reproducible reversed phase High Performance Liquid Chromatographic (RP-HPLC) method was developed for the estimation of imatinib mesylate using PDA detector. The system consisted of RP-C18 column and the detection was performed at 260 nm. The mobile phase consist of (4ml tetrabutyl ammonium hydroxide and .01M ammonium dihydrogen orthophosphate (pH adjusted to 3 with orthophosphoric acid) and acetonitrile in ratio 60:40) pumped at room temperature and a flow rate of 1ml/min. Imatinib mesylate was eluted at 2.812min. The mean absolute recoveries of Imatinib mesylate was about 100.1% to 100.3% and the limit of detection (LOD) of imatinib was 10 µg/ml and the limit of quanitation (LOQ) is 20 µg/ml. the method shows good linearity in the range 20 µg/ml to 120 µg/ml (r2>0.995). The intra (n=6) and inter (n=6) day assay variations in the linear range is < 4 .Three marketed products containing imatinib mesylate are analyzed to test the applicability of the new method. The percentage of Imatinib mesylate in marketed preparations studied was found to be 99.58%, 99.92 and 100.85 respective to the label claimed[11].

A simple, specific and accurate reverse phase high performance liquid chromatographic method was developed for the determination of Imatinib mesylate and its amine Impurity in pharmaceutical dosage form. The column used was HiQSil C18 (250 x 4.6 mm, 5µm), with mobile phase containing methanol and Acetate Buffer pH 3.5 inthe ratio of 80: 20 v/v, the flow rate was 1.0 mL/ min and eluent was monitored at 273nm. The retention time for Imatinib mesylate was 8.071and for Amine Impurity it is 4.958. The proposed method was validated and successfully applied to the estimation of Imatinib mesylate and amine impurity in formulations[12].

This research work discusses about developing and validating a RP-HPLC method for the determination of selected anti-cancer drugs in bulk and pharmaceutical formulations using Trial and error method. Analytes were separated on a Onyx monolithic- C18 (100×4.6mm) with mobile phase comprising Potassium dihydrogen orthophosphate (0.01M), Methanol and

Acetonitrile in ratio of (30:30:40), with flow rate of 0.9 mL/min and pH: 4 adjusted with dilute orthophosphoric acid. Total chromatographic analysis time per samples was approximately 5 minutes with DST-Internal standard (IS), IMT, IBT and SFN eluting with retention times of 4.0, 4.78, 5.88 and 7.05 minutes respectively. Calibration curves were linear over selected range 0.997 for the all analytes. The method was sensitive with the LODs were 12.457, 13.07 and 29.169 ng/mL and LOQs were 43.68, 40.6 and 88.3ng/mL for IMT, IBT and SFN respectively. Inter and Intra-day precision data (in terms of %RSD) was fond to be less than ≥3 respectively, Recoveries ranged ≥102±2% for Imatinib- Gleevec, Ibrutinib- Imbruvica and Sorafenib- Nexavar. The obtained results corroborated the potential of the proposed method for determination of all the three anti-cancer dugs for routine analysis for products of similar type and composition[13].

A simple and sensitive high-performance liquid chromatography (HPLC) method was developed to quantitate imatinib in human plasma. Imatinib and the internal standard dasatinib were separated using a mobile phase of 0.5% KH_2PO_4 (pH3.5)–acetonitrile–methanol (55:25:20, v/v/v) on a CAPCELL PAK C18 MG II column (250 mm × 4.6 mm) at a flow rate of 0.5 mL/min and measurement at UV 265 nm. Analysis required 100 µL of plasma and involved a solid phase extraction with an Oasis HLB cartridge, which gave recoveries of imatinib from 73% to 76%. The lower limit of quantification for imatinib was 10 ng/mL. The linear range of this assay was between 10 and 5000 ng/mL (regression line r2 > 0.9992). Inter- and intra-day coefficients of variation were less than 11.9% and accuracies were within 8.3% over the linear range. The plasma concentrations of imatinib obtained by our present method were almost the same as those assayed by an LC–MS–MS method at the Toray Research Center, Inc. This method can be applied effectively to measure imatinib concentrations in clinical samples[14].

The popularity of imatinib in modern medicine has underscored the need for a fast and effective quantification method without the use of expensive instruments. The aim of this study was to develop and validate a relatively fast, cheap and effective HPLC method for the quantification of imatinib in human serum. This method uses a simple preparation step with an ExtrelutR NT 3 extraction tube and commercial available solvents. A Marcherey-Nagel Lichrospher 100-5 RP8 250 × 4 mm column held at 30°C, a mobile phase of 0.05 M H_3PO_4/KH_2PO_4 acetonitrile (7:3, v/v) at a flow rate of 1 mL/min and a diode array detector operated at a wavelength of 265 nm were used for the analysis of 50 µL prepared sample injected into the HPLC. A single run was completed in 15 min. The method presented here has a limit of quantification of 30 ng/mL and is linear between 0.1 and 10 µg/mL[15].

The main aim of present work was to develop a simple, precise, rapid and reproducible isocratic reverse phase high performance liquid chromatographic (RP-HPLC) method for the estimation of Imatinib in pure and in tablet dosage form. An isocratic RP-HPLC was performed by utilizing Welchrom C18 column, (250 mm × 4.6 mm i.d., particle size 5

µm) maintained at ambient temperature and mobile phase composed of a mixture of 10 mM Phosphate Buffer (pH- 3) Acetonitrile (50: 50 v/v). The flow rate was adjusted 1.0 mL/min and UV detection was performed at 264 nm. The retention time of Imatinib peak was found at 3.053 minutes. The developed method was linear in the range of 2- 10 µg/mL with correlation coefficient of 0.9999. The method was found to be specific and accurate with the overall mean % recovery of 99.85 %. The % RSD of intra and inter-day precision was found to be 0.833 and 0.877 respectively. The % RSD values were below two for intraday and inter- day precision indicated that the method was highly precise. The developed method was highly sensitive with LOD of 0.105 µg/mL and LOQ of 0.319 µg/mL. Assay content of Imatinib was determined and the mean % found for Imatinib was in good agreement with the label claim. The proposed method was statistically validated for its linearity, precision, accuracy, specificity, Robustness and ruggedness. The optimized methods proved to be specific, robust and accurate and can be used for quality control of Imatinib in bulk drug and pharmaceutical formulations[16].

A novel reverse phase liquid chromatographic method was developed and validated for estimation of chronic myelogenous leukemia and acute lymphocytic leukemia drug, imatinib mesylate in its API and dosage form i.e. tablets. The reverse phase HPLC analysis was carried out on isocratic system. The column was Peerless basic C18 (50mm x 4.6mm, 3µm) with ambient temperature. The mobile phase consisted of buffer: methanol in proportion 45: 55 % (v/v). The flow rate was maintained at 1ml/min. The detection was carried out at wavelength 266 nm. The method was validated as per ICH guidelines for system suitability, linearity, accuracy and precision. The linear ranges was observed as 50-150µg/ml for imatinib mesylate. The accuracy and precision were found to be well within the acceptable limit. The method was successfully applied for assay imatinib mesylate of in API and dosage form with good recoveries[17].

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, R^2 = 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[18].

A simple, sensitive high performance liquid chromatographic method was validated for the estimation of Imatinib Mesylate in pure and in pharmaceutical dosage forms. A 4.6-mm ×150-cm column that contains packing L1 (C18) was used with a mobile phase containing a mixture of Buffer: Aetonitrile: Methanol (50:25:25). The flow rate was 1.1 ml/minute and effluent was monitored at 230 nm. Calibration curve was plotted with a range from 40-160 mg/ml for Imatinib Mesylate. The assay was validated for the parameters like specificity, linearity, range, precision, accuracy and robustness parameters. The proposed method can be useful in the routine analysis for the determination on Imatinib Mesylate in pharmaceutical dosage form[19].

The present study is to develop a simple, specific, and validated reverse-phase high-performance liquid chromatography (HPLC) method for the determination of imatinib mesylate and its dimer impurity in pharmaceutical dosage form. A HPLC instrument incorporated with column HiQ Sil C18 (250 mm × 4.6 mm, 5 µm), mobile phase as methanol and acetate buffer pH 3.5 in the ratio of 80:20 v/v was used for the determination of the imatinib mesylate and its dimer impurity. The detection wavelength was set at 273 nm. The flow rate of the mobile phase was 1.0 mL/min. The retention time for imatinib mesylate was 8.060, and for dimer impurity, it was 11.398. The calibration plot was linear (R^2=0.9971) and the % mean recoveries for imatinib mesylate were in the range of 99.83–101.57, and for dimer impurity, it was in the range of 98.16–99.18. The limit of detection concentration was found to be 0.570 µg/ml for imatinib mesylate and 0.033 µg/ml dimer impurity and limit of quantification concentration was 1.728 µg/ml for imatinib mesylate and 0.099 µg/ml dimer impurity. The projected method was validated and successfully functional for the estimation of imatinib mesylate and dimer impurity in formulations. It can be adopted apparently for routine quality control and research tests[20].

The aim of this paper was to develop and validate the stability indicating RP-HPLC method for the determination of Imatinib mesylate in bulk and pharmaceutical dosage forms. A simple, accurate, precise, sensitive and stability indicating RP-HPLC method has been developed for the determination of Imatinib mesylate in bulk drug and pharmaceutical dosage form, in which separations are done using develosil C18, 5µm, 150 × 4.6mm i.d. column at a flow

rate of 1.0mL/min with an injection volume of 20µL. The beer's law was obeyed over the concentration range of 5 - 35µg/mL. The correlation coefficient was found to be 0.996 and it showed good linearity, reproducibility, precision in this concentration range. The % recovery values were found to be within the limits, which showed that the method was accurate. The LOD and LOQ were calculated using statistical methods. The % RSD values were less than 2. The developed method was successfully applied for determination of Imatinib mesylate in pharmaceutical dosage form. The results obtained are in good agreement with those obtained by using the standard method[21].

The present research work describes a rapid and accurate RP-HPLC for estimation and validation of Imatinib mesylate in tablet dosage form. It is used in the treatment of chronic myeloid leukemia. The separation of drug was achieved by on Phenomenex column (4.6 mm X 150 mm i.d) 5µ column. The mobile phase consists mixture Orthophosphoric buffer (pH 2.5): Methanol (50:50). The detection was carried out at a wavelength 263nm. The method was validated as per ICH guidelines for system suitability, linearity, accuracy, precision, robustness and stability of sample solution. The linear ranges for Imatinib mesylate were 10-50 µg/mL, 0.072-2.4 µg/mL respectively with good recoveries i.e., 100.5%[22].

An accurate, precise, simple and economical RP-HPLC method has been developed for the rapid estimation of Imatinib Mesylate in pure and pharmaceutical formulation. The separation was achieved on C18 (cosmosil), column (250 × 4.6 mm i.d 5 µm) using Acetonitrile : O-Phosphoric acid (0.1 % v\v) 60:40 as mobile phase, at a flow rate of 1.0ml/min. Detection was carried out at 264nm & drug eluted with a retention time of 6.08 min. Beer's law was obeyed in the concentration range of 10-50µg\ml. with correlation coefficient 0.999. The method has been validated according to ICH guidelines for linearity, accuracy, repetability, precision, robustness, ruddgedness, LOD & LOQ. The method was found to be specific, accurate & precise, robust & sensitive. The proposed method was convenient for quantitative routine analysis of Imatinib Mesaylate in bulk & pharmaceutical dosage form[23].

Imatinib mesylate has been a breakthrough treatment for chronic myeloid leukemia. It has become the ideal tyrosine kinase inhibitor and the standard treatment for chronic-phase leukemia. Striking results have recently been reported, but intolerance to imatinib and noncompliance with treatment remain to be solved. Molecular monitoring by quantitative real-time polymerase chain reaction is the gold standard for monitoring patients, and imatinib blood levels have also become an important tool for monitoring. A fast and cheap method was developed and validated using high-performance liquid chromatography-mass spectrometry for quantification of imatinib in human serum and tamsulosin as the internal standard. Remarkable advantages of the method includes use of serum instead of plasma, less time spent on processing and analysis, simpler procedures, and requiring reduced amounts of biological material, solvents, and reagents. Stability of the analyte was also studied. This research also intended to drive the validation scheme in clinical centers. The method was validated according to the requirements of the US Food and Drug Administration and Brazilian National Health Surveillance Agency within the range of 0.500–10.0 µg/mL with a limit of detection of 0.155 µg/mL. Stability data for the analyte are also presented. Given that the validated method has proved to be linear, accurate, precise, and robust, it is suitable for pharmacokinetic assays, such as bioavailability and bioequivalence, and is being successfully applied in routine therapeutic drug monitoring in the hospital service[24].

The present investigation was aimed to establish a simple, accurate and highly sensitive validated stability-indicating liquid chromatographic method for imatinib mesylate. The purpose was to develop a method to detect nanogram quantity of the drug specific in development of nanoparticles. Imatinib mesylate was successfully analysed in a broad range from 50 to 50,000 ng/ml on Develosil® ODS-HG-5, Nomula chemical (50 mm×4.6 mm) analytical column, using 55:45 (v/v) aqueous (pH 8) to organic phase ratio (methanol and acetonitrile, 6:4) as the mobile phase, at a flow rate of 1.0 mL/min and detection at 267 nm with a good linearity (R2 > 0.9992). The method was validated for precision, accuracy, robustness, sensitivity and specificity. The method was further utilized to evaluate the fate of imatinib mesylate under various stress conditions including acid, alkaline, oxidation and photo degradation. The method was highly specific to determine pure drug from the degraded products. Further, it was inferred by the results that imatinib is less labile to alkaline and photo degradation[25].

A novel, simple and economic reverse phase High Performance Liquid Chromatography (RP-HPLC) method has been developed for the quantification of Imatinib in bulk and capsule dosage form with greater precision and accuracy. Separation was achieved on Analytical technologies, C-18, (250mm × 4.6mm) column in isocratic mode with mobile phase consisting of acetonitrile: potassium dihydrogen phosphate buffer (pH 2.5) (30:70v/v) with a flow rate of 0.8 mL/min. The detection was carried out at 268 nm. The retention time of Imatinib was found to be 2.67 min. The method was validated as per ICH guidelines. Linearity was established for Imatinib in the range 5-35 µg / ml with r^2 value 0.996. The percentage recovery of Imatinib was found to be in the range 99.49-99.67 %. The high recovery and low relative standard deviation confirm the suitability of the proposed method for the estimation of the drug in bulk and capsule

dosage forms. Validation studies demonstrated that the proposed RP-HPLC method is simple, specific, rapid, reliable and reproducible for the determination of Imatinib for quality control level[26].

A simple and sensitive High Performance Liquid Chromatographic method has been established and validated for Imatinib Mesylate in pharmaceutical dosage form, separation was performed on a C18, 150 × 4.6 mm, 5µ column in isocratic mode, with mobile phase containing a mixture of buffer: acetonitrile (72:28 v/v). The mobile phase was pumped at a flow rate of 1.0 ml/min and eluents were monitored at 265 nm. Linearity was found to be in the range of levels 80% to 120% and retention time was 3.63 min. The statistical validation parameters such as linearity, accuracy, precision, and specificity, limit of detection, limit of quantification were checked. The samples were prepared in water and the stability of Imatinib mesylate in aqueous solution at 30°C was studied. The results were satisfactory with good stability after 24 h at 30°C. The proposed method can be used for the related substances of Imatinib mesylate[27].

A simple, rapid, reverse phase and stability-indicating high-performance liquid chromatography (HPLC) method for the estimation of imatinib in solution and in plasma under forced degradation conditions was developed. The method employed isocratic elution using a Waters Atlantis C18 (5 µ, 4.6 mm × 150 mm) HPLC column. The mobile phase consisted of acetonitrile and 10 mM KH_2PO_4 buffer in the ratio of 35:65 (v/v, pH = 4.6), which was delivered using isocratic flow at a rate of 1 mL/min. The injection volume of 50 µL and imatinib was monitored using UV detection 270 nm after a clean-up step with diethyl ether and with a total run time of 6 min. Results: The method was validated in solution as well as in plasma, and the response was found to be linear in the concentration range of 0.5-20 µg/mL. The coefficient of correlation was found to be >0.99. Forced degradation studies revealed that imatinib undergoes degradation under different stress conditions. Discussion: The developed HPLC method could effectively resolve degradation product peaks from imatinib except at neutral pH. Further, no interference was found at the retention time of imatinib from any plasma components, indicating selectivity of the developed method. The limits of detection and quantitation of the method were 0.025 and 0.5 µg/mL, respectively[28].

Tyrosine kinase inhibitors (TKIs) are effective in the targeted treatment of various malignancies. KIs including small molecue KIs and monoclonal antibodies directed against kinases, have emerged over the past decade as an important class of anticancer agents. Imatinib was the first to be introduced into clinical oncology, and it was followed by drugs such as gefitinib, erlotinib, sorafenib, sunitinib, and dasatinib. TKIs are also called tyrphostins, the short name for "tyrosine phosphorylation inhibitor", originally coined in a 1988 publication, which was the first description of compounds inhibiting the catalytic activity of the epidermal growth factor receptor (EGFR). Nibs are either in dosage form, blood serum, or biological fluids. This paper reviewes the reported analytical methods for the determination of Dasatinib, Lapatinib, Sorafenib, Imatinib, Nintedanib, Sunitinib, Pazopanib individually or in combination with other drugs are represented in tables 2-8. Table 9 is concerned with the reported methods for the combination of different members of Nibs[29].

RP-HPLC method was developed by Imatinib mesylate in bulk and pharmaceutical dosage form maximum absorbance was found at 230nm and peak purity was excellent. Imatinib mesylate is a protein-tyrosine kinase inhibitor, Inhibits the abnormally functioning Bcr- Ab1 tyrosine kinase which is produced by the Philadelphia chromosome abnormality found in chronic myeloid leukaemia (CML). It is found that the method of RP-HPLC with UV-detection system for the analysis of Imatinib mesylate is straight forward and applied in qualitative and quantitative analysis. This method is simple, rapid, selective and inexpensive. The percent recovery of drug ranged from 99.0 to 100.4. The proposed method for estimation of selected drug Imatinib mesylate was successfully applied in pharmaceutical formulation[30].

An accurate, precise, simple and economical RP- HPLC method has been developed for the rapid estimation of Imatinib Mesylate in pure and pharmaceutical formulation. The separation was achieved on C18 G column (250 x 4.6 mm i.d, 5 µm), using o-Phosphoric acid (0.1% v/v): Acetonitrile 70:30 (v/v) as mobile phase, at a flow rate of 1.0 ml/min. Detection was carried out at 266 nm and drug eluted with a retention time of 3.25 min. Beer's law was obeyed in the concentration range of 5-30 µg/ml with correlation coefficient 0.999. The method had been validated according to ICH guide lines for specificity, linearity, accuracy, precision, robustness, ruggedness, LOD and LOQ. The method was found to be specific, accurate, and precise, robust, rugged and sensitive. The proposed method was convenient for quantitative routine analysis and quality control of Imatinib Mesylate in bulk and pharmaceutical dosage form[31].

Imatinib mesylate is used to treat various cancerous diseases. Lately, investigations have focused on the enhancement of chemotherapeutic agents. Thus, rifampicin is a promising candidate due to its chemosensitizing potential beyond its anti-infectious effects. In this study, a reliable separation method for imatinib mesylate and rifampicin have been developed. The HPLC analysis were performed on a C18 column (150 x 4.6 mm, 3 µm particle size) at 25 °C. The best UV decetection was observed at 254 nm. The mobile phase was set as acetonitrile and

TEA/phosphate buffer (pH: 7.04; 0.1 M) (50:50, v/v) with isocratic elution. The flow rate was set as 0.8 mL/min. The method validation was performed according to the international guidelines with respect to selectivity, linearity, precision and accuracy, recovery and sensitivity. The detection and quantification limit of the method were 0.63 μg/mL and 1.90 μg/mL, respectively for imatinib mesylate, and 3.04 μg/mL and 9.22 μg/mL for rifampicin. The method was linear in the range of 10–90 μg/mL with determination coefficients (r2≥0.99) for both drugs. Precision, accuracy and recovery values (RSD<3%) of the method was convincing. Considering the various usage of imatinib mesylate and rifampicin, the developed method is applicable to different dosage forms[32].

A simple, sensitive high performance liquid chromatographic method was validated for the estimation of Imatinib Mesylate in pure and in pharmaceutical dosage forms. A 4.6-mm X 150-cm column that contains packing L1 (C18) was used with a mobile phase containing a mixture of Buffer: Aetonitrile: Methanol (50:25:25). The flow rate was 1.1 ml / minute and effluent was monitored at 230 nm. Calibration curve was plotted with a range from 40-160 mg/ml for Imatinib Mesylate. The assay was validated for the parameters like specificity, Linearity, Range, precision, accuracy & robustness parameters. The proposed method can be useful in the routine analysis for the determination on Imatinib Mesylate in pharmaceutical dosage form[33].

A study was conducted on Relative Response Factor by changing the High Performance Liquid Chromatography (HPLC) chromatographic method conditions like different HPLC columns, Flow rate, pH, Temperature, Buffer concentration, Detector wavelength, different Detectors (Ultraviolet & Photo Diode Array Detectors) and different Solvent grades and observed the variations in established RRF. The authors have studied the impact on RRF by changing the Robustness parameters and HPLC columns and all the results were compared. The comparision study has shown that any slight variations in method conditions, the impact is observed on established RRF values[34].

A novelreverse phase liquid chromatographic methodwas developed and validated for estimation of chronic myelogenous leukemia and acute lymphocytic leukemia drug, imatinib mesylate in its API and dosage form i.e. tablets. The reverse phase HPLC analysis was carried out on isocratic system. The column was Peerless basic C18 (50mm x 4.6mm, 3μm) with ambient temperature. The mobile phase consisted of buffer: methanol in proportion 45: 55 % (v/v). The flow rate was maintained at 1ml/min. The detection was carried out at wavelength 266 nm. The method was validated as per ICH guidelines for system suitability, linearity, accuracy and precision. The linear ranges was observed as 50-150μg/ml for imatinib mesylate. The accuracy and precision were found to be well within the acceptable limit. The method was successfully applied for assay imatinib mesylate of in API and dosage form with good recoveries[35].

A sensitive HPLC method has been developed for the assay of imatinib in human plasma, by off-line solid-phase extraction followed by HPLC coupled with UV-Diode Array Detection. Plasma (750 μl), with clozapine added as internal standard, is diluted 3+1 with water and subjected to a solid-phase extraction on a C18 cartridge. After matrix components elimination with 2000 μl of water (in two aliquots of 1000 μl), imatinib is eluted with 3×500 μl MeOH. The resulting eluate is evaporated under nitrogen at room temperature and is reconstituted in 180 μl 50% methanol. A 50 μl volume is injected onto a Nucleosil 100–5 μm C18 AB column. Imatinib is analyzed using a gradient elution program with solvent mixture constituted of methanol and water containing both 0.05% ammonium acetate. Imatinib is detected by UV at 261 nm. The calibration curves are linear between 0.1 and 10 μg/ml. The limit of quantification and detection are 0.05 and 0.01 μg/ml, respectively. The mean absolute recovery of imatinib is 96%. The method is precise with mean inter-day CVs within 1.1–2.4%, and accurate (range of inter-day deviations −0.6 to +0.7%). The method has been validated and is currently being applied in a clinical study assessing the imatinib plasma concentration variability in a population of chronic myeloid leukemia- and gastro-intestinal stromal tumor-patients[36].

5. UV- Visible methods

The present work deals with development of two rapid, precise and accurate spectrophotometric methods for the estimation of Imatinib Mesylate in bulk and solid dosage form. Method A is area under the curve in which wavelength range 237-277nm was selected for estimation of Imatinib Mesylate . Method B is area under the curve in which wavelength range 400-800nm was selected for estimation of Imatinib Mesylate . Linearity was observed in the concentration range 2-10μg/ml for both the methods (r2=0.9992 for method A and method B). The results of analysis have been validated statistically, which confirm the accuracy and reproducibility of the methods. All the methods were found to be simple, precise and accurate and can be employed for routine quality control analysis of Imatinib Mesylate in bulk as well as in its solid dosage form[37].

A simple and precise spectroscopic method for determination of Imatinib Mesylate in its bulk and tablet dosage forms has been developed and validated. This method based upon measurement of light absorption in UV region. The UV spectra of Imatinib Mesylate showed that maximum absorbance of light was observed at 281 nm and linearity was

observed in the concentration range of 2-28ug/ml with correlation coefficient 0.999. The proposed method was validated as per ICH Q2 (R1) guidelines for linearity, accuracy, precision and recovery. The limit of detection (LOD) and limit of quantitation (LOQ) were found to be 0.040468 (µg/ml) and 0.122263 (µg/ml) respectively by simple UV Spectroscopy[38].

A simple, rapid, precise and highly selective spectrophotometric method was developed for estimation of imatinib in tablet dosage form this method, involves the measurement of absorbances of imatinib at the wavelength of 255.20 nm distilled water was used as solvent. linearity was observed in the concentration range of 2-12µg/ml for imatinib the accuracy of the method was confirmed by recovery studies of tablet dosage forms and was found to be 101.2% for imatinib.the method showed good reproducibility and recovery with % RSD less than 6 the LOD of imatinib was found to be 0.066µg/ml and LOQ of imatinib was found to be 0.2µg /ml thus the proposed method was found to berapid, specific, precise, accurate and cost effective quality control tool for the routine analysis of imatinib in bulk and tablet dosage form[39].

A simple, fast, accurate and precise UV-spectroscopic method and RP-HPLC method were developed and validated for the estimation of Imatinib/Capecitabine per ICH guidelines. Acetonitrile and water (50:50) was used as the solvent. The λ max of Imatinib/Capecitabine was found to be 242 nm and it was proved linear in the concentration range of Imatinib 0.5-3µg/ml and for Capecitabine 1-6µg/ml with a correlation coefficient value of 0.999. Accuracy studies of UV-spectroscopy method was performed at three different levels, i.e., 50%, 100%, and 150% and recovery was found to be in the range of 99.6 to 100.8% for Imatinib and the range of 98.3 to 101.2% for Capecitabine respectively. The Limit of Detection (LOD) and Limit of Quantification (LOQ) were found to be 0.217 and 0.658 µg/ml for Imatinib and 0.103 and 0.312 for Capecitabine. RP-HPLC method was developed by using Acetonitrile: water, 0.1% ortho phosphoric acid (50:50). The method was developed in Eclipse C18 column (100 mm × 4.6 mm, 3.5µm particle size). In RP-HPLC method was found to be linear in the range of Imatinib/Capecitabine is 0.25-1.5µg/ml with a correlation coefficient value of 0.999. The accuracy studies of RP-HPLC method was performed at three different levels, i.e., 50%, 100%, and 150% and recovery was found to be in the range of 98.24 to 100.3% for Imatinib and the range of 98.18 to 99.98% and for Capecitabine respectively. The limit of detection (LOD) and Limit of Quantification (LOQ) were found to be 0.0421 and 0.1276 µg/ml for Imatinib and 0.047.and 0.1424 µg/ml for Capecitabine for RP-HPLC method. The % RSD is <2% which indicates the accuracy and precision of the method. The above method was a rapid tool for routine analysis of Imatinib/Capecitabine in the bulk and in the pharmaceutical dosage form[40].

The present work deals with development of two rapid, precise and accurate spectrophotometric methods for the estimation of Imatinib Mesylate in bulk and solid dosage form. Method A is first order derivative spectroscopy where derivative amplitudes were calculated by considering minima and maxima of the curve. Method B is area under the curve in which wavelength range 237-277nm was selected for estimation of Imatinib Mesylate. Linearity was observed in the concentration range 5-30µg/ml for both the methods (r^2=0.9992 for method A and r^2=0.9996 for method B). The results of analysis have been validated statistically, which confirm the accuracy and reproducibility of the methods. All the methods were found to be simple, precise and accurate and can be employed for routine quality control analysis of Imatinib Mesylate in bulk as well as in its solid dosage form[41].

A simple, rapid, precise and highly selective spectrophotometric method was developed for Estimation of imatinib in tablet dosage form this method, involves the measurement of absorbances of imatinib at the wavelength of 255.20nm distilled water was used as solvent. linearity was observed in the concentration range of 2-12µg/ml for imatinib the accuracy of the method was confirmed by recovery studies of tablet dosage forms and was found to be 101.2% for imatinib the method showed good reproducibility and recovery with % RSD less than 6 the LOD of imatinib was found to be 0.066µg/ml and LOQ of imatinib was found to be 0.2µg /ml thus the proposed method was found to be rapid, specific, precise, accurate and cost effective quality control tool for the routine analysis of imatinib in bulk and tablet dosage form[42].

Two simple, sensitive and rapid spectrophotometric method for the determination of imatinib (β-form) in pure as well as in pharmaceuticals were described. The proposed methods are based on the formation of ion association complexes of the drug with BCG and BTB, which were measured at absorption maximum of 414nm and 416nm respectively. Beer's law was obeyed in the concentration ranges 10.0 to 50µg/ml for BCG and BTB methods, respectively. Other statistical analyses such as Student's t test and F test values are studied for both the proposed methods and the results were with that of the reported spectrophotometric methods. Basing on the results the proposed methods can be successfully applied for the assay of imatinib(β-form) in various forms of pharmaceuticals[43].

Two new simple, sensitive and cost effective visible spectrophotometric methods were developed for the estimation of imatinib mesylate in both bulk drug samples and formulations. The first method (method A) was based on the oxidative

coupling of the drug with the reagent namely 3-methyl-2-benzothiazolinone hydrazone and ferric chloride solution. The second method (method B) was based on the formation of ion pair complex of the drug with an acidic dye namely bromocresol green in acidic buffer solution followed by their extraction in chloroform. The absorbance of the chromogens was measured at the absorption maxima of 569 nm for mehod A and 417 nm for mehod B against the corresponding reagent blank. The method obeyed Beer's law between 25-350 µg/mL for 3-methyl-2-benzothiazolinone hydrazone and 5.0- 40 µg/mL for bromocresol green.The results of recovery experiments indicated average recovery was above 99.81 %. The interference studies also revealed the common excipients and other additives usually present in pharmaceutical dosage forms did not interfere in the proposed methods[44].

A Simple and precise UV-spectroscopic method was developed for the determination of Imatinib Mesylate in its bulk and formulation. The developed method has been validated for various parameters like specificity, accuracy, linearity, robustness according to USP general chapter<1225> and ICH Q2R1 guidelines. Pure solution of Imatinib Mesylate was scanned in the whole range of UV region where it has shown the maximum absorbance at 258nm. The RSD values for method precision and intermediate precision were found to be well within the acceptance criteria and the series of dilutions were found to be linear (2-12ug/ml) where r2= 0.999 was the regression value. Limit of detection (0.2925µg/ml) and Limit of quantification (0.8977µg/ml) of IMT were established. Further, the drug has been subjected to various stress conditions, and percent degraded was reported. Drug solutions have shown stability on the benchtop for up to 8 hours and 72 hours when the solutions were refrigerated[45]

6. Conclusion

The collected methods are various analytical methods for the estimation of Imatinib which is an anticancer drug. The drug can be estimated by using HPLC method, UV method, colorimetric method in single as well as in combined dosage form. This collection may be use full for quick glance of various analytical methods for estimation of Imatinib.

Compliance with ethical standards

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Disclosure of conflict of interest

No any conflict of interest.

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