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REVIEW ARTICLE **OPEN ACCESS**

A Brief Review on Developed Analytical Methods for Estimation of Imatinibin Pharmaceutical Formulation

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ABSTRACT
Imatinib mesylate is an anti-cancer drug that is used to treat chronic myelogenous leukemia (CML), gastrointestinal stromal tumors (GIST)and some other malignancies. It is the first member of a new class of agents that act by inhibiting specific tyrosine kinase enzymes rather than by non-specific inhibition of rapidly dividing cells. Anticancer drugs can act on cancer cells, endothelium, extracellular matrix, immune system, or host cells at different levels. Pharmacokinetic studies of anticancer drugs on cancer patients are of great importance for dose selection and dosing intervals in clinical applications. Imatinib is an oral chemotherapeutic drug used to treat cancer. It is marketed under the trade names Gleevec and Glivec (100, 400mg) in capsule and tablet dosage forms distributed globally by Novartis. Imatinib (small chemical inhibitor) targets several receptor tyrosine kinases, including CSF1R, ABL, c-KIT, FLT3 and PDGFR specifically, it is used for some types of gastrointestinal stromal tumors (GIST), chronic eosinophilic leukemia (CEL), hypereosinophilic syndrome (HES), systemic mastocytosis and myelodysplastic syndrome that are Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) and acute lymphocytic leukemia (ALL). The purpose of this overview is to compile a comparative study of various analytical methods from various sources like PubMed, ScienceDirect, google scholar, reference books and research articles to determine drug identification, purity, physical properties and potency including investigations of bioavailability and its stability. Current review articles can be effectively scrutinized for future analytical studies of imatinib estimation.
Keywords: *Imatinib, anti-cancer drug, analytical methods, Purity study.*

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INTRODUCTION

The number of drugs entering the market is increasing every year. These drugs may be new entities or partial restructuring of assets vary the launch date is often delayed. Uncertainty about their continued and widespread use of the drug may report new toxicity (resulting in the withdrawal of drugs from the market) or the development of patient resistance by competitors and the introduction of better drugs. Under these standard and analytical conditions, the actions of these drugs may not be available in the pharmacopeia. So, it becomes necessary to develop new analytical methods for these drugs and also important in medicines because it commits life [1,2].

During the 1990s Nicholas Lyndonaa chemist operating for Ciba-Geigy made-up imatinib, Associate in nursing its use to treat CML was driven by Brian Druker, a medical specialist at the Dana-Farber Institute. STI57 was the name given to imatinib, a 2-phenylaminopyridline spinoff while it changed into below early development. Signal Transduction Inhibitor (STI) represented the drug that might inhibit enzymes known as tyrosine kinase inhibitors. In 1998 the first scientific trial of imatinib took place and the drug received FDA approval in May 2001. Laskar-DeBakey received a Clinical Medical Research award in 2009 for changing a deadly most cancers right into a potential condition changed into provided to Lyndon, Druker and different Colleagues and in 2012, the Japan Prize for his or her part in the development of a new therapeutic drug focused on most cancers-specific molecules [3].

Imatinib mesylate is described chemically as 4-[(4-methyl 1-piperazinyl)methyl]-N-[4-methyl-3-[4-(3-pyridinyl]amino]-phenyl]benzamide methane sulphonate is a white to off -white to brownish/yellowish tinged crystalline in nature. It has a formula of $C_{30}H_{35}N_7SO_4$ and a relative molecular mass of 589.7gm/mol. It is freely soluble in water, slightly soluble in ethyl alcohol (96%) and insoluble in dichloromethane[4]. The drug is designed to inhibit tyrosine kinases including BCR-ABL and is used withinside the remedy of continual myeloid leukemia (CML) and gastrointestinal stromal tumors [5].

Imatinib Mesylate is the latest anticancer agent and is used asa priority among various cancer remedies prescribed to deal with leukemia and epithelial duct tumors. It functions by inhibiting proteins related to

neoplastic cell growth to get relief. Imatinib mesylate is one of the medications within the market place and become one of the first medications to be driven through the Food and drug administration's (FDA) rapid tune designation for its approval [6].

CLINICAL PHARMACOLOGYOF IMATINIB

Tyrosine kinases are important mediators of signaling cascades that plays a key role in various biological processes such as growth, differentiation, metabolism and apoptosis in reaction to external and internal stimuli. Deregulation of protein kinase activity has been shown to play a central role in pathogenesis of human cancers. Imatinib, a 2-phenylaminopyrimidine derivative, is a tyrosine kinase inhibitor with activity against ABL, BCR-ABL, PDGFRA (platelet-derived growth factor receptor alpha gene) and c-KIT(CD117). Each active center of tyrosine kinases contains a binding site for ATP. The enzyme activity catalyzed by tyrosine kinases is transfer of terminal phosphate from ATP to tyrosine residues on substrates, a process known as protein tyrosine phosphorylation. It inhibits enzymatic activity of proteins in a semi-competitive manner by binding tightly to ATP-binding site and in a closed or self-associated conformation [7].

Many protein kinases are down regulated associated many are overexpressed in human cancers [8,9]. It reserved the constitutively active fusion product arising from the metropolis (Ph) body of chronic myelogenous leukemia (CML) and c-kit (CD117), that was overexpressed in gastrointestinal stromal tumor (GIST). Aminoalkanoic acid kinases have an active website for binding ATP. Transfer of the terminal phosphate from nucleotide to aminoalkanoic acid residues on its substrates causes macromolecule tyrosine phosphorylation, which leads to the activation of signal-transduction pathways. Drug damages BCR-ABL-mediated transfer of phosphate to its substrates and works by binding near the ATP binding site, lockup it during a closed or self-inhibited conformation, therefore it inhibits catalyst activity of protein semi-competitively, ultimately ensuing in -switching -off downstream signal pathways that support leukemogenesis [10].

In an oral toxicity study in rats for 13 weeks, intermittent renal calcification and mild bladder mucosal hyperplasia were observed at lowest dose of 6 mg/kg. In dogs, no effect was observed at 3 mg/kg, but progressive hepatotoxicity was observed at highest dose of 100 mg/kg. Some episodes of vomiting, diarrhea, mild anemia and neutropenia have also been observed at the highest dose level. Designing a phase I or II study to assess tolerability based on preclinical data, examine pharmacokinetic properties of the compound and look for preliminary indications of efficacy. These studies have been ongoing since June 1998 and focus on her CML patient in the chronic phase who was refractory to interferon therapy. Treatment with STI 571 is given as a daily oral treatment [11].

PHARMACOKINETICS OF IMATINIB

After oral administration the bioavailability of drug was 90% [12], Pharmacokinetic studies of imatinib in healthy volunteers and patients with CML, GIST and other cancers showed that orally administered imatinib was well absorbed regardless of the oral dosage form (solution, capsule, tablet) or dose, which has been shown to have an absolute bioavailability of 98% (100mg, 400mg). Food has no relevant effect on the rate or degree of bioavailability. The terminal elimination half-life is approximately 18 hours. Imatinib is approximately 95% bound to human plasma proteins, mainly to albumin and α1-acid glycoprotein. The active substance is excreted mainly in the bile as metabolites, one of which (CGP 74588) shows pharmacological activity equivalent to that of the parent compound. The fecal-urine excretion ratio is approximately 5:1 [13].

The main metabolite, N-demethylated anthelminthic derivative, was also active, intended predominant by CYP3A4. It showed efficiency almost like the imatinib. The plasma FTO for this substance was concerning 15% of the FTO for imatinib. The half-lives were 13.5± 0.9hr for imatinib, 20.6 ± 1.7hr for N desmethyl metabolite. Gall and fecal matter were the foremost route of elimination and completely a tiny low portion of the drug was excreted within the urine. Most of the imatinib was eliminated as metabolites and completely 25% was eliminated as unchanged [3].

ANALYTICAL METHODS REPORTED FOR IMATINIB

The projected method is predicated on the concentration of mild absorption in the UV region in distilled water. The UV spectrum of Imatinib mesylate in distilled water showed λmax at 256nm. Beer's law is valid within the concentration vary of 2-12µg/ml. This method was validated for precision, accuracy, ruggedness and robustness. Applied statistical analysis proves that the method is reproduce and selective for the estimation of the stated drug [14].

2.A simple and accurate spectroscopic method for the determination of imatinib mesylate in its bulk and tablet dosage forms has been developed and validated. This method is based on the measurement of light

absorption in the UV region. The UV spectrum of imatinib mesylate showed this maximum absorption of light was observed at 281nm and linearity was observed in the concentration range of 2 to 28µg/ml with a correlation coefficient of 0.999. The proposed method has been validated against ICH Q2 (R1) guidelines for linearity, precision, accuracy and recovery. The detection limit (LOD) and the limits of quantification (LOQ) by simple UV spectroscopy were found to be 0.040468 (µg/ml) and 0.122263 (µg/ml), respectively [15].

3. simple, rapid, accurate, and reproducible high-performance reversed-phase liquid chromatography method was developed for the estimation of imatinib in large-scale pharmaceutical formulations. Quantification was performed using a Develosil C18 column (150 × 4.6 mm ID, particle size 5 µm) in isocratic mode, with a mobile phase consisting of buffer (NaH_2PO_4, pH adjusted to 8.0 with triethylamine: methanol: acetonitrile mobile phase (55:27:18 % v/v/v). The flow rate was 2.0ml/min and detection were performed at 240nm. The drug retention time was found to be 8.2-52 minutes and the method produced a linear response over a concentration range of 12-36µg/ml (R^2-0.9998). Restoration studies were also performed and the %RSD (Relative Standard Deviation) reproducibility was found to be 0.601. The proposed method has been statistically evaluated and can be used for routine quality control analysis of imatinib tablets [16].

4.An accurate, simple and cost-effective high-performance liquid chromatography method has been developed for the estimation of imatinib mesylate in tablet dosage forms. The method thus developed is a reverse-phase high-performance liquid chromatography method using a Hypersil BDS C18 column (length: 250nm, diameter: 4.6nm, particle size: 5µm) and a simple buffer of ammonium phosphate and acetonitrile (40:60v/v) as the mobile phase. The thus-developed method was validated according to regulatory guidelines using a well-developed analytical method validation tool that includes analytical method validation parameters such as linearity, accuracy, method precision, specificity, system suitability, and robustness. The results obtained were within acceptable criteria [17].

5.Current research describes fast and accurate RP-HPLC estimation and validation of imatinib mesylate in tablet form. The used in treatment of chronic myeloid leukemia separation from the drug was obtained on a Phenomenex column (4.6mm x 150mm; 5µ column). The mobile phase consists of an ortho phosphorus buffer mixture (pH2.5): methanol (50:50). A detection was found the wavelength is 263nm. The method has been validated according to the ICH guidelines for system suitability, linearity, accuracy, precision robustness, and stability of the sample solution. The linear range of imatinib mesylate recovery rates was good, 10-50µg/ml and 0.072-2.4µg/ml, respectively this is 100.5% [18].

6. An accurate, simple and cost-effective RP-HPLC method was developed for the rapid estimation of Imatinib mesylate in pure pharmaceutical formulation. Separation was performed on a C18 G column (250 x 4.6mm, 5 µm), o-phosphoric acid (0.1%v/v): acetonitrile 70:30 (v/v) as mobile phase, flow rate1.0ml/min. Detection was performed at 266 nm and the drug eluted with a retention time of 3.25 minutes. The beer law was observed in the concentration range of 5-30 µg/ml with a correlation coefficient of 0. 999.Method confirmed according to ICH guidelines for specificity, linearity, precision, accuracy, robustness, ruggedness, LOD and LOQ. The method proved to be specific, accurate and precise, robust and sensitive. The proposed method is suitable for routine quantitative analysis and quality control of imatinib mesylate in bulk and pharmaceutical-grade dosage forms [19].

7.An inverse phase gradient HPLC method with a PDA detector was developed for the purity and evaluation of imatinib mesylate in a bulk drug. Impurities include (2-methyl-5-aminophenyl)-4-(3-pyridyl)-2-pyrimidine amines (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 an Inertsil ODS 3V column (150 x 4.6 mm, 5 µ) stationary phase with a column oven temperature of 35°C and UV detection at 268 nm. The separation was achieved using a gradient buffer program (one of the buffers used was 0.1% triethylamine in water, pH adjusted to 2.9 with glacial acetic acid) and mixtures of methanol and acetonitrile. This method was adapted based on the peak size and resolution of Imp-A and Imp-B. The method was verified under (ICH) guidelines in terms of the limit of detection (LOD), the limit of quantification (LOQ) and linearity, precision, accuracy, specificity, robustness and stability of the solution. The values of LOD and LOQ were found 0.024µg/ml and 0.08µg/ml respectively. The concentration of the injected sample was 10mg/ml. The method is linear in the range of 0.08-0.3µg/ml for both impurities [20].

8. The drug is designed to inhibit tyrosine kinases such as BCR-ABL. Developed and validated a simple, rapid, accurate and precise UV spectroscopic method and RP-HPLC method for estimation of Imatinib/Capecitabine as per ICH guidelines. Acetonitrile and water (50:50) were used as the solvent. The λ max of imatinib/ capecitabine was 242 nm and was shown to be linear with a correlation coefficient of 0.999 over the concentration range of imatinib 0.5–3 µg/ml and capecitabine 1–6 µg/ml. Accuracy studies of UV-vis spectroscopy method were performed at three different levels of 50%, 100%, 150% and recovery was found to be between 99.6 to 100.8% for imatinib and between 98.3 to 101.2% for capecitabine

respectively. The limit of detection (LOD) and limit of quantification (LOQ) were 0.217 and 0.658µg/ml for imatinib and 0.103 and 0.312 for capecitabine. An RP-HPLC method was developed using acetonitrile: water, 0.1% (50:50) orthophosphoric acid. The method was developed on an Eclipse C18 column (100 mm × 4.6 mm, particle size 3.5 µm). The RP-HPLC method was found to be linear in the imatinib/ capecitabine range from 0.25 to 1.5 µg/ml with a correlation coefficient of 0.999.A precision study of the RP-HPLC method was performed at three different concentrations, namely 50%, 100%, 150%, and the recoveries were 98.24% to 100.3% for imatinib and 98.18% to 99.98%, respectively % for capecitabine paddy field. Limits of detection (LOD) and limits 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 the method RP-HPLC. The %RSD is less than 2%, demonstrating the accuracy and precision of the method. The above method has been a rapid tool for routine analysis of imatinib/capecitabine in bulk and pharmaceutical dosage forms [21].

9.A simple, rapid, accurate, and powerful isocratic reverse-phase liquid chromatography solution method has been developed and validated for the determination of imatinib in tablet dosage forms. Chromatographic separations were performed using an ACE Phenyl (150mm x 4.6mm) 5 column as the stationary phase with isocratic elution of buffer preparation (2.88gm disodium hydrogen phosphate dissolved in 1000ml water and pH was adjusted). pH adjusted to 2.7 with orthophosphoric acid and methanol as mobile phase in a ratio of 400:600 v/v. The flow rate was set at 1.0 ml/min and UV detection was performed at 265nm. The injection volume was 5µl. The column oven temperature was maintained at 50°C. The sample temperature was maintained at 25°C. The retention time of imatinib was approximately 3.4 minutes. The linearity of the drug was maintained in a concentration range of 20,000-120,000µg/ml. This method can be used in routine quality control samples during manufacture and in real-time analysis of stability samples [22].

10. A simple, rapid, accurate and highly selective spectroscopic method was developed to characterize imatinib in tablet form. This method involves measuring the absorbance of imatinib at a wavelength of 255.20 nm. Distilled water was used as a solvent. Linearity was observed in a concentration range of 2-12 µg/ml for imatinib. The accuracy of this method was confirmed by a recovery study of the tablet formulation, which was 101.2% for imatinib. This method demonstrated good reproducibility and recovery with an RSD of less than 6%. The imatinib LOD was found to be 0.066 µg/ml and the imatinib LOQ was 0.2 µg/ml. Therefore, the proposed method is a fast, specific, accurate, precise and cost-effective quality control tool for routine analysis of imatinib in bulk and tablet dosage forms [23].

11. A new, simple and sensitive UV spectrophotometric method has been developed for the determination of imatinib mesylate in bulk and pharmaceutical formulations (tablets and nanoparticles). The developed spectroscopic methods were validated for selectivity, linearity and range, accuracy, precision and sensitivity. This method has demonstrated excellent linearity in the range of 2.5-25µg/ml with the regression equation: Absorbance (AU) = 0.047 x Concentration (µg/ml) + 0.008 and R2 = 0.9998. The developed method showed high recovery (99-102%) and low relative standard deviation (lt;5%) at 285 nm. Furthermore, the method was found to be sensitive at the lower limits of detection (0.57µg/ml) and quantification limits (1.71µg/ml). The apparent molar absorptivity and sandal sensitivity were found to be 2.75 x 10(3) L/m cm and 2.15µg/cm^2, respectively. The validated method was successfully used to analyze the active ingredient content in tablets and nanoparticle formulations. Furthermore, this method has been successfully used for pH metric solubility analysis of drugs [24].

12.A reverse-phase HPLC method with UV detection was developed to estimate bulk imatinib. Quantification was performed on a C18 column, GEMINI (250mm, 4.6mm) as stationary phase in isocratic mode and mobile phase containing a mixture of acetonitrile, methanol and formic acid in a ratio of 35:60:05 (v/v/ v). The flow rate and detection wavelength were set to 1.0 ml/min and 229nm respectively. The drug retention time was found to be 3.46 minutes and the production method was linear over the concentration range of 30-100µg/ml. Recovery studies have also been performed at different concentrations. The proposed method was validated in terms of linearity, precision, LOD, LOQ, accuracy and robustness according to the ICH guidelines [25].

13.Two simple, sensitive and rapid spectrophotometric methods for the determination of imatinib (form) in pharmaceutical and pure formulations are disclosed. The proposed methods are based on the formation of ionic binding complexes of the drug with BCG and BTB measured at an absorbance of 414nm and 416 nm, respectively. Beer's law was followed at concentrations ranging from 10.0 to 50µg/ml for the BCG and BTB methods, respectively. Other statistical analyses such as Student's t-test and F-test values were studied for both proposed methods and the results were consistent with reported spectrophotometric methods. Based on the results, the proposed methods can be successfully applied for the determination of imatinib (β-form) in different pharmacological forms [26].

14.A simple and rapid isocratic reverse-phase high-performance liquid chromatography (RP-HPLC) method has been developed and validated for the determination of imatinib in purified form. The drug

imatinib has been exposed to a variety of stressful conditions. The proposed method has been shown to exhibit stability through forced dissolution experiments and mass balance studies. Chromatographic separation was performed using a 5µ (150mm x 4.6mm) Eclipse XDB-C18 analytical column as a stationary phase with isocratic elution of a mobile phase mixture of 1.5g sodium dihydrogen phosphate in 500ml of water and pH adjustment to 8.00. Triethylamine (buffer preparation): A mixture of 300ml volume of methanol and 200ml of acetonitrile was prepared. Mixed at a ratio of 450:550 v/v at a flow rate of 1.0ml/min. The shaft furnace temperature was maintained at 50°C. The sample temperature was kept at room temperature. The injection volume was set at 20µl and the detector was performed at 265nm.The half-life of imatinib was approximately 5.5 minutes. The linear concentration range ranged from 19.815 to 29.722µg/ml with correlation coefficients of 0.9999. The method developed was validated as per the ICH guidelines [27].

15.Two new simple and effective colorimetric methods have been developed to determine imatinib (mesylate) in pure and pharmaceutical formulations. Charge transfer (CT) interaction between imatinib as electron donor and 2,3-dichloro-5,6, dicyano-p-benzoquinone (DDQ) and chloroanilic acid (CAA) as π-electron acceptor. The resulting charge transfer complexes were measured at λmax of 462 nm and 537nm for DDQ and CAA respectively, in methylene chloride. Different variables affecting the response were studied and optimized. In optimal conditions, Beer's law was observed in a drug concentration range of 0.25-3.50 mg/10ml and 0.50-5.50mg/10ml when using DDQ (0.4% w/v) and CAA (0.3% w/v) with correlation coefficients of 0.996 and 0.998 respectively. The proposed methods showed good linearity, precision and reproducibility, and validity was assessed using standard summation techniques with an average percent recovery of 99.90 ± 1.36 in the case of DDQ and 100.20± 0.91 in the case of CAA [28].

16.Sensitive and selective liquid mass a spectrophotometric liquid-tandem chromatography (LC-MS/MS) method was developed and validated for analysis of trace amounts and (GT;1ng/ml of 2-methyl-5-aminophenyl)-4-(3-pyridyl)-2-pyrimidine. (Imp-A) Genotoxic impurities in imatinib mesylate.LC-MS/MS analysis of Imp-A on a 5µm (150mm x 4.6mm) Inertsil C18 column using 0.1% formic acid in 1000 ml water as a buffer in mobile phase A and acetonitrile in mobile phase B was carried out. The Gradient program is developed for quick analysis. The flow rate was 1.0 ml/min and the elution was monitored by a mass spectrophotometer. The method was validated by the conference according to International Harmonization (ICH) guidelines. LC-MS/MS for quantification of 1ng/ml Imp-A [29].

17. A simple, rapid, selective and quantitative HPTLC method was developed and validated for the determination of imatinib mesylate in bulk and tablet dosage forms. Samples of imatinib mesylate were applied to an aluminum TLC plate pre-coated with silica gel GF254 and developed using methanol: chloroform (8:2 v/v) as the mobile phase. The bands at λ = 279 nm were scanned with a Camag TLC 3 scanner and detected and quantified with a UV detector. The Rf value was found to be 0.22. The linearity was in concentration range of 50-300ng per point and recovery rate was 96.55%. The limit of detection and limit of quantification was 16.36ng per point and 49.59ng per point, respectively. The coefficient of determination (r^2) was 0.9996. The regression equation was y = 17,209x + 63,798. The method was also validated for precision, specificity and recovery. This developed method was used to analyze commercially available formulations [4].

18.A recent publication reported that imatinib forms adducts of cyanide and methoxylamine in vitro, but the exact structure was not determined. This study reports the identification of seven cyanide adducts that may elucidate bioactivation pathways and provide insight into the observed clinical side effects of the drug. Imatinib was incubated with human liver microsomal proteins in presence of the NADPH regeneration system and reduced scavengers GSH, potassium cyanide, and methoxylamine. Samples were analyzed by high-performance liquid chromatography (HPLC) coupled to an LTQ-Orbitrap data acquisition system. Chemical composition determination and or data-dependent tandem mass spectrometry (MS(n)) in positive and negative scan modes, as well as hydrogen and deuterium exchange (HDX), are assumed based on accurate mass measurements. The conjugates of GSH and methoxylamine were not identified or were insufficient for their characterization. However, seven cyanide conjugates were identified, indicating that the partial piperazine and p-toluidine structures of imatinib are biologically active and can be captured by nucleophilic cyanide ions. Reactive intermediates are assumed to be the imine and imine-carbonyl (α, β-unsaturated) conjugated structures of the piperazine ring and imine-methide of p-toluidine moiety. Chemical structures of seven imatinib cyanide adducts were determined or suggested from high-resolution MS/MS data [30].

19.Imatinib mesylate has been a breakthrough treatment for chronic myeloid leukemia. It has become an ideal tyrosine kinase inhibitor and standard treatment for chronic phase leukemia. Surprising results have been reported recently, but imatinib intolerance and non-adherence to treatment have not been addressed. Molecular monitoring by real-time quantitative PCR is the gold standard for patient monitoring and imatinib blood levels have become an important monitoring analytical tool [31].

20. Measurement of imatinib plasma concentrations is useful in evaluating patient adherence to daily oral therapy, potential drug-drug interactions, treatment efficacy and serious drug-related side effects. The aim of this study was the correlation between two different methods of blood level testing, HPLC-UV and LC-MS/MS. here, analysis of 162 plasma samples from patients treated with imatinib were carried out. Finally, the quantification of imatinib was associated with molecular response genetic data in the follow-up study of patients with chronic myeloid leukemia were done [32].

21.A new method using high-performance liquid chromatography coupled with electrospray mass spectrometry to quantify PBMC concentrations of the tyrosine kinase inhibitors imatinib, dasatinib, and nilotinib were studied. A simple PBMC isolation and extraction procedure was applied to 10-14ml blood samples. Chromatographic separation of drugs and internal standard (quinoxaline) was achieved using a gradient (acetonitrile and water + 0.05% formic acid) on an analytical C18 reverse phase column with an analytical run of 25minutes at a flow rate of 0.25ml/min. All compounds' average intraday and intraday accuracies were 8.76 and 12.20%. The average accuracy was -3.86%. The extraction yield was 79–91%. The calibration curve ranges from 50.0 to 0.25ng. The limit of quantification was set at 0.25ng for all drugs tested. This newly developed method allows specific, sensitive and reliable intracellular simultaneous identification of three tyrosine kinase inhibitors imatinib, dasatinib and nilotinib in a single chromatographic step, which is useful for drug quantification in PBMCs of patients with chronic myeloid leukemia [33].

22.Imatinib, a competitive inhibitor of BCR-ABL tyrosine kinase, is currently the first-line treatment for chronic myeloid leukemia (CML). Therapeutic drug monitoring targeting through plasma levels of approximately 1000ng/ml can help optimize treatment efficacy. Here, the development of a high-performance liquid chromatography (HPLC) method with UV/diode array (DAD) detection to determine the concentration of imatinib in human plasma. Plasma trough concentrations of imatinib were measured in around 65 patients with chronic myelogenous leukemia using the developed method and LC-MS/MS as the reference method. The results of these two methods were compared using Deming's regression, chi-square test and sign test. The calibration curve was made in blank human plasma. HPLC-UV/DAD calibration curves were linear from 80 to 4000ng/ml and the limit of quantification was set at 80 ng/ml. The daily variance was 6.1%, the recovery after direct plasma protease was over 96% and the recovery from the column was over 98%. It has been observed that there is no significant difference in plasma levels of imatinib between HPLC-UV/DAD and LC-MS/MS. This HPLC-UV/DAD method was sufficiently specific and sensitive for imatinib TDM, with no evidence of interference. A rapid and inexpensive HPLC-UV/DAD method requiring only commonly available equipment is suitable for screening of imatinib in plasma [34].

23. This study aimed to validate and compare HPLC and LC-MS-MS analysis methods and their applicability for the quantification of imatinib in human plasma. The study enrolled 50 patients with chronic phase (CP) chronic myelogenous leukemia (CML) who were scheduled to receive imatinib 400 mg/day. Drug levels were determined by HPLC-UV and LC-MS-MS. The intraday HPLC accuracy was between 100.51 and 103.19%. The accuracy of LC-MS-MS ranged from 89.72 to 106.29%. The correlation coefficient for both methods was (r^2) = 0.96. HPLC can be used to accurately and precisely determine imatinib levels in patients [35].

24. In addition to affecting the systemic bioavailability of the parent drug, drug metabolizing enzymes (DMEs) can produce bioactive and/or toxic metabolites of clinical importance. This study evaluation of the ability to simultaneously analyze parent drug and newly identified metabolites in patient plasma using liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). In addition, cases of resistance and rare but sometimes serious side effects have been reported with this therapy. Quantitative imatinib and its metabolites in plasma were determined by performing three steps. In vitro cultures were performed using human liver microsomes (HLM) or patient plasma samples. Simultaneous determination of plasma levels of imatinib and 14 metabolites in plasma samples from 38 patients. The methods were partially or cross-validated and found to allow accurate determination of metabolite concentrations when pure standards are not available. Preliminary results suggest that imatinib's disposition and metabolites are related to inter-subject variables and that divergent metabolite profiles may be revealed. This article highlights that LC-MS/MS methods can simultaneously capture a complete metabolic profile of drugs alongside standard therapeutic drug monitoring (TDM), enabling multiple correlation studies of clinical importance [36].

25.Analysis of signaling inhibitor imatinib in patient tumor tissue by LC and MS/MS is described in this method. The anticancer drug is eluted within 2 minutes by RP-C18 along with internal standard STI571-d8. A standard curve was generated in red blood cells (RBC). Sediment measurements were applied for the quantitative separation of erythrocytes. Sedimentometry was used for the quantitative separation of erythrocytes. There was no indication of signal inhibition by substances derived from the biological matrix. The range of determination in tumor tissue was within the range recorded for erythrocytes and plasma.

The assay is selective, sensitive and robust, supporting experimental applications in clinical oncology and routine use in animal studies. The LOD in tumor tissue was 4.5ng per gram [37].
26.A simple, rapid and robust assay method has been developed for the assay of imatinib in liquid human plasma. Tandem chromatographic mass spectrometry using electrospray ionization in positive ion mode. imatinib and labeled internal standards were extracted from plasma by simple protein precipitation. Chromatography separation was performed by isocratic elution of the mobile phase with 5.0mM ammonium format. Water - 5.0mM ammonium formate in methanol (30:70v/v) for 3.0min on the reverse stationary phase. Detection was performed using a triple tandem triple reaction monitor mass spectrometer. The developed method was validated with a limit of quantification of 10ng/ml. calibration curve was linear from 10 to 2000ng/ml (R^2 and GT; 0.99). Method validation parameters are approved. Basic the spiked samples and standard solutions were stable under storage and handling conditions. The reliable method was successfully used in the analysis of real samples and then in a pharmacokinetic study in 27 Healthy Korean male volunteers [38].

CONCLUSION

The current review provides a summary of the different analytical methods reported in the literature for the determination of Imatinib in bulk drug formulation. Analysis methods including chromatography, instrumentation, examination, conductance techniques and electrochemical methods were compiled, which is used to quantify large amounts of imatinib in a bulk pharmaceutical dosage form. From this study, it is revealed that some analytical methods are obtainable on HPLC and UV-visible spectrophotometry and few articles are available based on hyphenated methods and electrochemical methods. The data reported for the Imatinib analysis are HPLC with UV detection is the most commonly used technique for the determination of Imatinib in the pharmaceutical matrix. Furthermore, High-performance thin-layer chromatography, MS techniques can be used in LC, LC-MS, and LC-MS/MS methods are also reported for the quantification of imatinib.

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