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Development and Validation of Zero Order UV-Visible Spectrophotometry method for Assay and Dissolution Studies of Imatinib mesylate

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Abstract: Imatinib (STI-571, Gleevec, Glivec, CGP 57148) is a protein-tyrosine kinase inhibitor that targets the ABL family of proteins. Imatinib is a drug that is used to treat some kinds of leukemia, as well as other malignancies and blood cell diseases. Imatinib also treats several forms of gastrointestinal stromal tumors (GIST). This study presents a new Zero-order Absorbance UV-Spectrophotometric approach for determining Imatinib Mesylate in commercial tablets and during dissolution tests that is simple, easy, accurate, precise, economical, and sensitive. It was possible to determine the concentration of Imatinib Mesylate in commercial tablets using 0.1N HCl at a λmax of 234 nm in a linear range of 3-18 g/mL with an R2> 0.99 and recovery between 99.27 and 99.72 %. The % amount of drug estimated in the developed method was found to be in good agreement with the label claimed in commercial tablet formulation. The technique was also optimized for quantifying Imatinib mesylate in dissolution tests in the same linear concentration range. This procedure has the advantage that it allows direct measurement of samples from the dissolution vessel without any pH correction. Further, the method has been validated for accuracy, precision, sensitivity, and ruggedness as per ICH guidelines.

Keywords: Imatinib mesylate; UV-Spectrophotometry; Dissolution studies etc.

1. Introduction

Imatinib mesylate (Gleevec®, Glivec®, formerly STI-571) is an oral anticancer agent rationally designed to selectively inhibit certain protein tyrosine kinases implicated in oncogenesis [1]. It is used in the treatment of multiple cancers, most notably Philadelphia chromosome-positive (Ph +) chronic myelogenous leukemia [2]. Imatinib potently inhibits Bcr-Abl and blocks proliferation and growth of tumor cells expressing bcr-abl or v-abl [3]. A significant advantage of Imatinib is that it is effective when administered orally; many anticancer drugs are effective only when injected [4].

Imatinib mesylate (Figure 1) is defined chemically as 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide methanesulphonate[5]. Imatinib mesylate is appeared as a white to off white crystalline powder [6]. According to a literature review, the drug has been assessed using Liquid chromatography in pharmaceutical formulations [7 -15], UPLC [16], human plasma [17-23] and simultaneous in Human plasma [24-27], LC/MS [28-29]. Also detection in rat plasma [30], in cell culture [31] by HPLC method was reported. Spectrophotometry methods for analyzing bulk dose forms or pharmaceutical dosage forms [32-34]. In-vitro, in-vivo drug release study was done by HPLC, UV [35-36].

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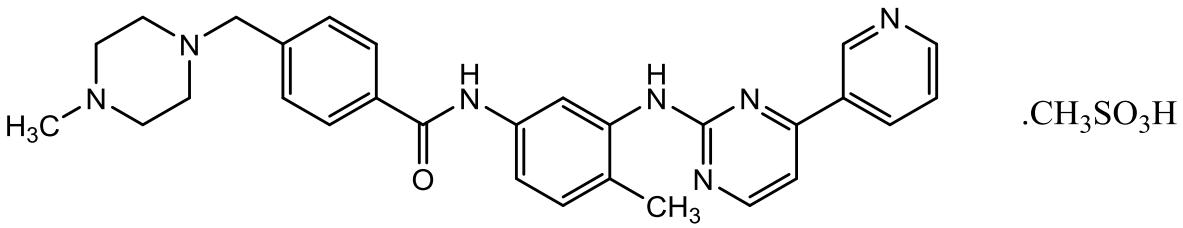

Figure 1. Imatinib Mesylate

The goal of this study was to create and verify a simple, precise, sensitive, and specific spectroscopic approach for Imatinib Mesylate in both bulk and tablet form.

2. Materials and Methods

2.1 Pharmaceutical standard.

Imatinib Mesylate (99.58%) of the pharmaceutical grade was supplied as a generous gift sample from Intas Pharmaceuticals Ltd., Ahmedabad, India.

2.2 Chemicals and reagents.

Chemicals and reagents of an analytical grade used. HPLC grade water and Hydrochloric acid were acquired from Merck, Mumbai, India.

2.3 Marketed formulation.

Imat® tablets labeled to encompass 100 mg/tablet; it was manufactured by Cadila Healthcare and distributed by Zydus Oncosciences, India.

2.4 Instrumentation.

A double beam UV-VIS spectrophotometer model-UV-2450 (Shimadzu, Japan) with quartz cells of 10 mm path length, connected to HP well-matched computer. The data analysis was performed on UV Probe 2.21. The weighing determination was performed with the assistance of Shimadzu electronic balance, model- Shimadzu AUX 120. The dissolution tests were performed using Electrolab Dissolution Tester (TDL-08L).

2.5 Selection of diluents.

After studying the stability and solubility of Imatinib mesylate in various solvents and in view to perform the dissolution test, the 0.1N hydrochloric acid is selected as solvent for the investigation.

2.6 Preparation of stock standard solution.

The stock standard solution was prepared by solubilizing the 10 mg of Imatinib mesylate in the 100 ml 0.1N HCl to obtain the 100 µg/mL concentration of Imatinib mesylate.

2.7 Preparation of working solution.

The specific aliquot (1.0 mL)was moved from stock standard solution into 10.0 mL of a volumetric flask; the volume was concluded to the mark with the same to obtain the 10.0 µg/mL concentration of Imatinib mesylate.

2.8 Stability of working solution.

The Imatinib mesylate solution of concentration 10.0 µg/mL was kept in dark at room temperature (25 ± 5 ^{o}C). The outcomes were documented at a chosen wavelength measured for six consecutive days with a 03 h interval. The mean, SD, and RSD % was estimated.

2.9 Spectral measurement of Imatinib mesylate.

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The spectral measurement of Imatinib mesylate was executed using the working solution of IMA. The resulting solution was assessed against the 0.1N HCl as a blank over through the UV region wavelength range of 200 – 400 nm. The IMA peak maximum absorbance of the zero-order spectra was observed at 234.00 nm.

2.10 Development of Calibration Curve.

Into a series of 10.0 mL volumetric flasks, different aliquots equivalent to 0.3 – 1.8 mL of IMA were moved out from the standard solution, and then the volume was completed to the point with 0.1 N HCl to obtain the required 3 – 18 µg/mL concentration ranges for IMA. The concentrations that resulted were then analyzed using the protocol described above. The responses of each solution were reported to determine the linear relationships between IMA concentrations and absorbances as responses.

2.11 Analysis of pharmaceutical matrices.

The designed approach wasapplied for the analysis of IMA in the marketed pharmaceutical preparation (Imat® Tablets, Zydus Oncosciences, India). Twenty tablets were weighed and finely grounded into powder. Tablet powder equivalent to 100 mg of IMA was precisely weighed and transferred into 100 mL volumetric flask and dissolved in 70 mL of 0.1 N HCl. Volume of was concluded to the mark. The resulting solution was ultrasonicated for the 20 min, filtered using 0.45 µm membrane filter, and to obtain the 1 mg/mL concentration. Further, the solution was diluted with the 0.1N HCl to get the desired concentration of IMA and was explored for spectral measurement as described earlier. The amount of drug in Imat® tablets was determined using linear equations of IMA.

2.12 Validation of the method.

The process of ensuring that the findings of a planned investigation are accurate, reliable, and specific to the ultimate goal of a structured analytical investigation is known as validation. To ensure accurate spectrophotometric analysis for investigating drug components in pharmaceutical matrices must always be validated. As a result, the proposed research has been validated in terms of accuracy, precision (intra-day, inter-day, and repeatability), sensitivity, and ruggednessas per the ICH guidelines Q2R1.

2.13 Accuracy.

Accuracy investigation for developed method was assisted as % recovery studies. It was performed at three different levels using the standard addition technique i.e.80, 100, and 120 %. The specified claimed standard IMA was added to the pre-investigated IMA tablet solution. The proposed method then re-examined it.

2.14 Precision.

Precision investigation of themethod was confirmed for intra-day, inter-day, and repeatability assay precision. The intra- and inter-day assay precision was confirmed using assessing the nine determinations of 6, 9, and 12µg/mL IMA concentrations on the same day of analysis (i.e., morning, afternoon, and evening) and for successive three days. At the same time, assay precision of repeatability study was addressed with 9µg/mL IMA concentration.

2.15 Sensitivity.

Sensitivity of the method was investigated using the standard deviation of the response and the slope. Detection Limit (DL) and Quantitation Limit (QL) were calculated using the

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formulae of DL = 3.3 × SD/S and QL = 10 × SD/S. The six estimations of calibration plots were selected to determined lower detection and Quantitation limits of IMA.

2.16 Ruggedness.

Ruggedness of the proposed method was determined by six determinations of aliquots from homogenous slot by two analyst using identical operational and environmental conditions.

2.17 In-vitro Dissolution Study.

A dissolution testing apparatus (ELECTROLAB DISSOLUTION TESTER TDL-08L) was used to determine *in-vitro* release rate of imatinib mesylate from Imatinib mesylate tablets. The dissolution test was performed using 900 mL of 0.1 N HCl at 37 ± 0.50°C and 75 rpm according to the Indian Pharmacopeia (IP) Dissolution testing apparatus I (paddle) method. The tablet was placed inside the dissolution vessel. 5 ml of sample were withdrawn at time intervals of 10, 20, 30, 40, 50 and 60 minutes. The withdrawn volume was replaced with 5 ml of fresh dissolution medium. The solutions' absorbance was then measured using a UV-Visible double beam spectrophotometer (SHIMADZU), model UV-2450 at 234 nm. Cumulative percentage drug release was calculated based on the standard curve.

To determine the mechanism of drug release from the tablet, the findings of the in-vitro dissolution study were fitted into the following kinetic equations:

1. Zero order drug release: Cumulative % drug release Vs Time.
2. First order drug release: Log cumulative % drug retained Vs Time.
3. Higuchi's classical diffusion equation: Cumulative % drug release Vs Square root of time.
4. Hixson-Crowell cube root law: Cube root of cumulative % drug retained Vs time
5. PeppasKorsemeyer Model: Cumulative % drug release Vs Log time.

3. Results and Discussion:

Imatinib mesylate is an anticancer drug that is specifically developed to inhibit certain protein tyrosine kinases that are involved in oncogenesis. The most difficult task that every pharmaceutical quality control researcher encounters is developing a reliable and repeatable spectrophotometric approach for measuring the analyte of interest from pharmaceutical matrices. The goal of the research reported here was to develop a simple, quick, and unique spectrophotometric method for determining IMA in tablets and conducting dissolution studies. The conventional approaches have used more comprehensive ranges of the calibration curve and wavelength of analysis; the developed novel zero order absorbance approach was found to be more sensitive and precise to estimate the IMA in the range of 3 – 18 µg/mL. Moreover, the proposed work explored 0.1 N HCl as a substitute to organic solvents, which is more economical than methanol and ethanol, thus considered to eco-friendly solvent. Wherefore, the developed spectrophotometric approach have become more environmentally sustainable than the previously documented reports. The applicability and reproducibility of proposed approach for routine quality control analysis of IMA was addressed by determining the stability of IMA in a 0.1N HCl solvent. The same was verified with keeping the 9 µg/mL working solution of IMA for 4 days; neither formation of precipitate nor change in color of 9 µg/mL solution of IMA was noticed; further, there was no significant dropdown of absorbance recorded at specified wavelength. The zero-order

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spectrum of IMA was recorded as shown in **Figure 2**, demonstrated maximum absorbance at 234.00 nm.

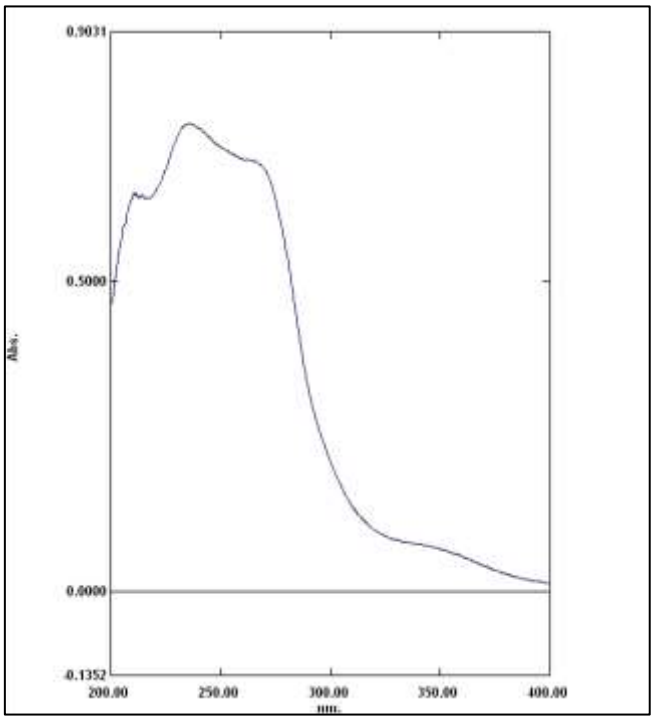

Figure 2. UV-Spectrum of Imatinib Mesylate in 0.1N HCl

For Linearity studies using 3-18 µg/mL concentrations of IMA it was found to be linear response with coefficient of correlation more than 0.99 for the developed approach as depicted in **Figure 3**.

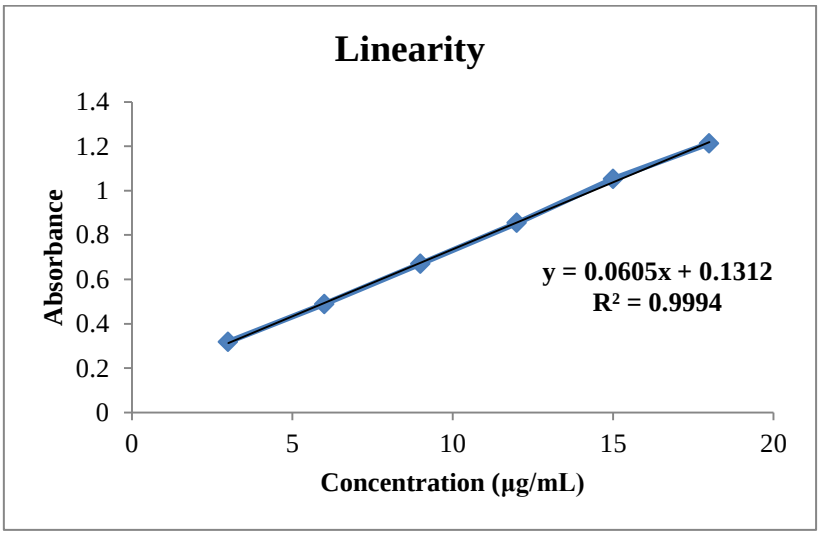

Figure 3. Imatinib calibration curve at 234.20 nm

The analytical findings of the calibration plots, including correlation coefficient, slope, and intercept, are summarized in Table 1. Detection Limit and Quantitation Limit for IMA were determined reported in Table 1 confirms the better sensitivity of the proposed approach.

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Table 1. Optical and regression parameters for UV-Spectrophotometric estimation of IMA

Sr. No.	Parameters	UV-Absorbance Method
1	λ max/AUC wavelengths (nm)	234.00
2	Beer's Law Limit (µg/mL)	3.00 – 18.00
3	Slope (S)	0.0605
4	Intercept (C)	0.1312
5	Determination coefficients (r^2)	0.9994
6	LOD (µg/mL)	0.62
7	LOQ (µg/mL)	1.88

The matrix of a tablet containing IMA (100 mg/tablet) (Imat® tablets), when analysed with the proposed method, proved to be excellent. The percent amount of IMA in the tablet matrix was found to be 99.69 ± 0.33 for proposed approach. As a result, no components of the matrix were found to interact with IMA. Thus, the proposed approach can be used to study IMA in a pharmaceutical quality control matrix.

The selectivity and specificity were also verified with RSD values less than 2% for three replicates, indicating that no interferences of the excipients were observed under these conditions with the determination of IMA in Imat® as presented in Table 2.

Table 2. Quantification of IMA from marketed matrix

Drug	Brand Name	Label claim	Amount found %	% RSD (n=6)
Imatinib mesylate	IMAT®	100 mg	99.69	0.33

*n- number of estimations

Precision was assessed as intra-day precision, inter-day precision, and repeatability assay. It was examined using concentrations of 6, 9, and 12 µg/mL with a repeatability assay at 9.0 µg/mL, indicating that the % RSD was less than 2%, representing that the proposed approach was accurate.

Table 3. Precision Studies (Intra-day, Inter-day) for IMA

Concentration (µg/ml)	Intra-Day		Inter-Day	
	% Amount found	%RSD (n = 3)	% Amount found	%RSD (n = 3)
6.00	99.25	0.32	99.74	0.89
9.00	99.77	0.46	99.21	0.65
12.00	99.80	0.87	99.57	0.74

*n = number of estimations

The findings obtained in Table 4 demonstrated superior accuracy of approaches that were evaluated by carrying out the standard addition technique on Imat® tablets at 80, 100, and 120 % levels, presented a good recovery rate at the levels studied, and it was found that % RSD is less than 2 for optimized approach that meet the requirements for acceptance of an accuracy study.

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Table 4. Recovery studies for IMA

Drug	Initial Amount [µg/ml]	Amount added [µg/ml]	Amount recovered [µg/ml, n = 3]	% Recovery	% RSD
IMA	6	4.8	9.52	99.36	0.92%
	6	6	10.98	99.72	0.70%
	6	7.2	12.31	99.27	0.57%

*n = number of estimations

The commercial brand Imat® was subjected to dissolution test and concentration of IMA was calculated by the optimized UV-Spectrophotometry approach. The dissolution behavior of IMA tablets was determined by finding the R^2 value for each release kinetic model following the Zero order, First order, Hixson-Crowell, Peppas Korsemeyer, and Higuchi models. The highest correlation coefficient (R^2) value, which was derived according to its respective kinetic model, indicated its pattern of release. Regression coefficient (R^2) values for different kinetic models and Dissolution Profile of Imatinib mesylate tablet depicted in Table 5 and Figure 4 respectively. The dissolution study for IMA tablets presented here shows R^2 value of first order model is very near to 1 than the R^2 values of other kinetic models. Thus, the drug release is considered to follow first-order kinetics.

Table 5. Regression coefficient (R^2) values for different kinetic models

Kinetic Model	Regression coefficient (R^2)
Zero order drug release	0.8250
First order drug release	0.9911
Higuchi's classical diffusion equation	0.9043
Hixson-Crowell cube root law	0.9572
PeppasKorsemeyer Model	0.9544

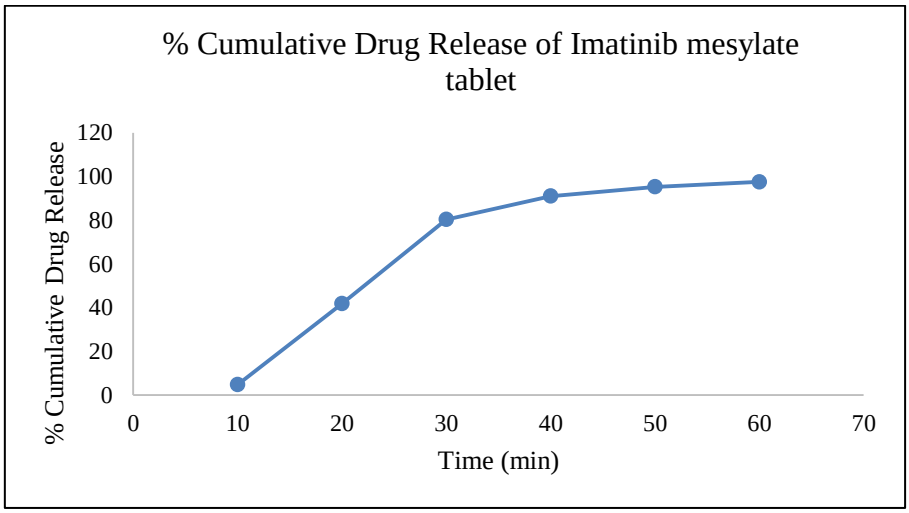

Figure 4. Dissolution Profile of Imatinib mesylate tablet

4. Conclusion

The accuracy was determined by the number of aliquots of a homogenous sample, which was determined by the adequate number of aliquots. The percent RSD was discovered to be in the

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region of 2.0. This demonstrated that the method's accuracy was enough. The findings demonstrated that the suggested approach was effective in recovering Imatinib mesylate. The developed method was proven to be successful and reliable to monitor dissolution studies. Hence, this approach may be used routinely in the quality control analysis and *in-vitro* dissolution studies of imatinib mesylate tablets.

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Conflicts of Interest

The authors declare no conflict of interest

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Abbreviations:
STI – 571 - Signal Transduction Inhibitor-571
IMA – Imatinib mesylate
HCl – Hydrochloric acid