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Research Article

Chemo-metric Assisted UV - Spectrophotometric Methods for the Estimation of Imatinib Mesylate-An Anti Cancer Drug

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Abstract

Imatinib mesylate is an anti-cancer agent used for the treatment of Myeloid leukemia. Three chemometric assisted UV-spectrophotometric methods have been developed for the estimation of Imatinib mesylate tablet formulations. A double beam UV-VIS spectrophotometer (Shimadzu Model No. UV-1800) was used for the study. Imatinib mesylate has shown linearity over the concentration range 1-30, 0.1-30 and 0.5-30 µg/mL in phosphate buffer (pH 8.0), borate buffer (pH 9.0) and in 0.1N hydrochloric acid solution in zero order as well as first order derivative spectrophotometric techniques. The proposed methods were validated as per ICH guidelines.

Keywords: Imatinib Mesylate; Derivative Spectroscopy; ICH Guidelines; Validation

Introduction

Imatinib mesylate is a leukemia medication for the treatment of chronic myeloid leukemia, an uncommon type of blood cell cancer that begins in bone marrow. The medication inhibits tyrosine kinase, there by blocking the action of the abnormal protein that signals cancer cells to multiply. On May 10, 2001, imatinib mesylate (Gleevec, formerly known as STI-571 and Glivec), manufactured and distributed by Novartis Pharmaceuticals, East Hanover, NJ (USFDA approved). Chemically Imatinib mesylate is methanesulfonic acid;4-[(4-methylpiperazin-1-yl)methyl]-N-[4-methyl-3-[(4-pyridin-3-ylpyrimidin-2-yl)amino]phenyl]benzamide with molecular formula $C_{30}H_{35}N_7O_4S$ and molecular weight of 589.7g/mol. Different analytical methods such as RP-HPLC (2-11), LC-MS/MS (12-16) and spectrophotometry (17-25) were reported in the literature. In present study the authors have proposed zero order and first order derivative spectrophotometric methods for the assay of Imatinib mesylate in three different buffer solutions and all the method were validated as per ICH guidelines.

Materials and Methods

Model No. UV-1780 double beam UV-VIS spectrophotometer (Shimadzu) with quartz cells is used for the entire study, and all the solutions were scanned at 200-400 nm. Reagent solutions phosphate buffer (pH 8.0) borate buffer (pH 9.0) and 0.1N hydrochloric acid solutions were prepared as per IP. Stock solution of Imatinib mesylate was prepared by dissolving 25 mg of API in 25 ml volumetric flask in methanol and sonicated (1000 µg/ml) and dilutions were prepared with phosphate buffer (pH 8.0) borate buffer (pH 9.0) and 0.1N hydrochloric acid solutions for Method I, II and III respectively in volumetric flasks from the stock solution.

Method validation

Linearity, Precision and accuracy studies

Zero-order spectroscopy (D_0)

A series of Imatinib mesylate solutions were prepared in phosphate buffer (pH 8.0) (1-30 µg/ml), borate buffer (pH 9.0) (0.1-30

µg/ml) and 0.1N hydrochloric acid (0.5-30 µg/ml) for Method I, II and III respectively and scanned (200-400nm) against their reagent blanks and the λ_{max} was found to be at 205 nm in all the three methods. A calibration curve was drawn by plotting the concentration on the X-axis and the corresponding absorbance on the Y-axis.

First-order derivative spectroscopy (D_1)

The individual zero-order absorption spectra so obtained for Imatinib mesylate were converted into first-order derivative spectra with the help of inbuilt software of the instrument and the resultant derivative spectra has shown minima at 284 nm and zero crossing points at 235.45, 256.55 nm. A calibration curve was drawn by plotting the concentration on the X-axis and the corresponding derivative absorbance (Minima value) on the Y-axis.

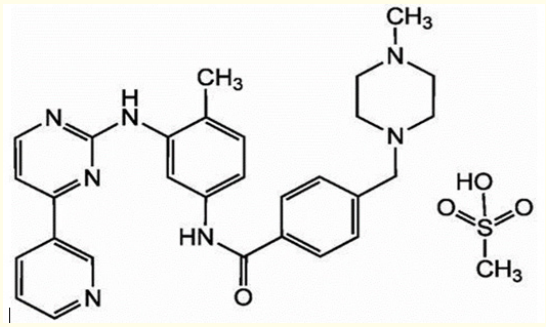

Figure 1: Chemical structure of Imatinib mesylate.

The intraday and interday precision studies were performed (n=6) at the concentration of 15 µg/ml and the acuracy stdies were carried out by the standard addition method (50%, 100%, 150%) and the % recovery was calculated.

Assay of Imatinib mesylate

Imatinib mesylate is available as tablets with brand names of Glivec (Label claim: 400 mg) (Novartis), Mitinab (Label claim: 400 mg) (Glenmark Pharmaceuticals), Imacure (Label claim: 100 mg) (Symbion Lifescience), Curevec (Label claim: 100 mg) (Mediclone) etc.

Twenty tablets were procured from the local pharmacy store, weighed, powdered and powder equivalent to 25 mg of Imatinib mesylate was extracted with methanol in a 25 ml volumetric flask and dilutions were made in three different reagents described earlier and the assay was carried out as explained above.

Results and Discussion

Two different analytical techniques such as zero-order and first-order derivative spectroscopy were developed for the estimation of Imatinib mesylate (tablets). The analytical methods so developed in the literature were summarised in Table 1.

Table 1: Literature survey.

Method	Mobile phase/Reagent	Reference
HPLC	Acetonitrile: Water	[2]
HPLC	Methanol: Water	[3]
HPLC	Methanol: Phosphate buffer	[4]
HPLC	Acetonitrile: 0.02 M with 0.2% Triethylamine	[5]
HPLC	Mixture of buffer: Acetonitrile	6]
HPLC	Methanol: Water: Triethylamine	[7]
HPLC	Ammonium phosphate buffer: Acetonitrile	[8]
HPLC	Acetonitrile: Ammonium acetate buffer	[9]
HPLC	Sodium heptane sulphonic acid in 0.01 M KH_2PO_4 (pH 2.5): Methanol	[10]
HPLC	0.02 M Phosphate buffer: Acetonitrile	[11]
LC-MS-MS	Acetonitrile: Ammonium formiate buffer	[12]
LC-MS-MS	0.1% aq. Formic acid: Methanol	[13]
LC-MS-MS	Water: Acetonitrile: Formic acid	[14]
LC-MS-MS	5.0 mM aq. Ammonium formate: 5.0 mM Ammonium formate in Methanol	[15]
LC-MS-MS	Methanol: Water containing 0.1% Formic acid and 0.2% Ammonium acetate (55:45)	[16]
Spectrophotometry	Reagent	Reference
Spectrophotometry	Distilled water	[17]
Spectrophotometry	Distilled water	[18]
Spectrophotometry (Derivative spectroscopy)	Distilled water	[19]

Spectrophotometry	Water, Methanol Acetonitrile, 0.1 N HCl 1.1 N NaOH Phosphate buffer (pH 1–13)	[20]
Spectrophotometry	0.1M HCl	[21]
Spectrophotometry	Distilled water 0.1M HCl	[22]
Spectrophotometry (Charge transfer complexation)	2,3-Dichloro-5,6,-dicyano-p-benzo quinone (DDQ) Chloranilic acid	[23]
Spectrophotometry	Distilled water	[24] (AUC and Zero order)
Spectrophotometry	Oxidation of drugs by Ce	[25] (Colorimetry)
Spectrophotometry (Zero order and First order derivative spectroscopy	Phosphate buffer (pH 8.0) Borate buffer (pH 9.0)0.1N Hydrochloric acid	Present methods

Zero-order spectroscopy (D_0)

The absorption spectra obtained in phosphate buffer (pH 8.0) (Method I), borate buffer (pH 9.0) (Method II) and 0.1N HCl solution (Method III) were shown in Figure 2. Imatinib mesylate has shown absorption maxima (λ_{max}) at 205 nm in all the three methods Beer-lambert's law was obeyed over the concentration range 1-30 µg/ml, 0.1-30 µg/ml and 0.5-30 µg/ml for Method I, II and III repsectively (Table 2) and the Calibration curves with regression equations were shown in Figure 3 and the optical characteristics were shown in Table 3. The percentage RSD in precision and accuracy studies was found to be less than 2.0 and all the three methods were found to be precise and accurate.

First order derivative spectroscopy (D_1)

The overlay first-order derivative spectra of Imatinib mesylate in phosphate buffer, borate buffer and 0.1N HCl solutions were shown in Figure 4. Beer-lambert's law was obeyed over the concen-

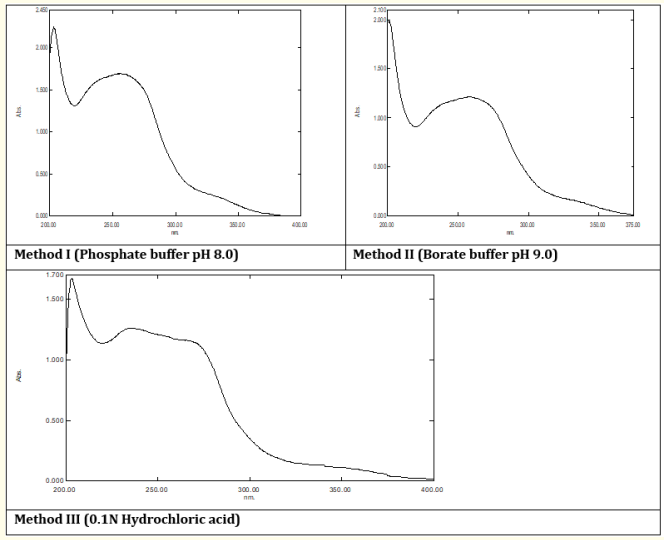

Figure 2: Absorption spectra of Imatinib mesylate (Zero order spectroscopy).

Table 2: Linearity (Zero-order spectroscopy).

Conc.(µg/ml)	Absorbance at λ_{max} (205 nm)		
	Method I	Method II	Method III
0.1	-	0.008	-
0.2	-	0.019	-
0.5	-	0.039	0.062
1	0.064	0.070	0.105
2	0.169	0.156	0.187
5	0.374	0.405	0.436
10	0.742	0.808	0.815
15	1.118	-	-
20	1.496	1.564	1.480
25	1.856	-	-
30	2.247	2.324	2.208

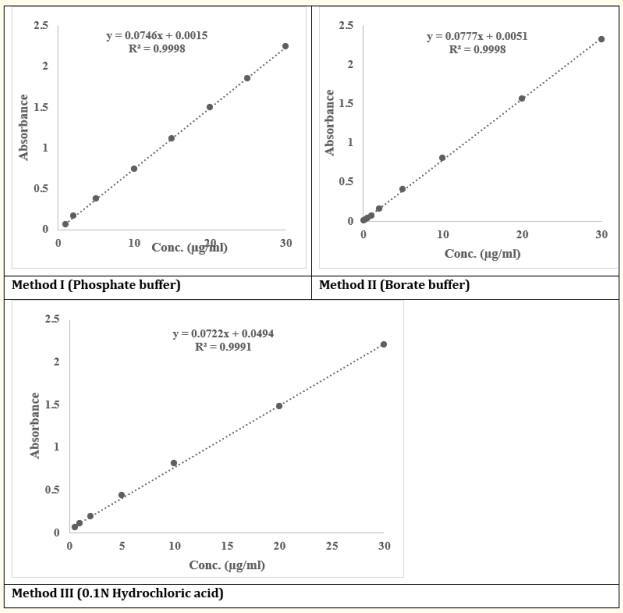

Figure 3: Calibration curves of Imatinib mesylate (Zero order spectroscopy).

Table 3: Optical characteristics (Zero order spectroscopy).

Parameters		Method		
		A	B	C
λ_{max} (nm)		205	205	205
Linearity range (µg/ml)		1-30	0.5-30	0.5-30
Molar extinction coefficient(litre/mole/cm^{-1})		4.375×10^{4}	4.764×10^{4}	4.81×10^{4}
Sandell's sensitivity(µg/cm^2/0.001 absorbance unit)		1.3477×10^{-2}	1.2376×10^{-2}	1.2269×10^{-2}
Slope		0.0746	0.0777	0.0725
Intercept		0.0015	0.0051	0.0473
Correlation coefficient		0.9998	0.9998	0.9994
Precision (% RSD)	Intraday	1.360	1.158	1.158
	Interday	1.160	1.156	1.157
Accuracy (% RSD)		0.315-0.58	0.29-0.15	0.32-0.45
Assay (%)		99	99.5	99.85

tration range 1-30 µg/ml, 0.1-30 µg/ml and 0.5-30 µg/ml for Method I, II and III repsectively (Table 4) and the calibration curves with regression equations were shown in Figure 5. The percentage RSD in precision and accuracy studies was found to be less than 2.0 and all the three methods were found to be precise and accurate. The percentage RSD value in precision and accuracy studies were found to be <2 indicating that all the methods are precise and accurate.

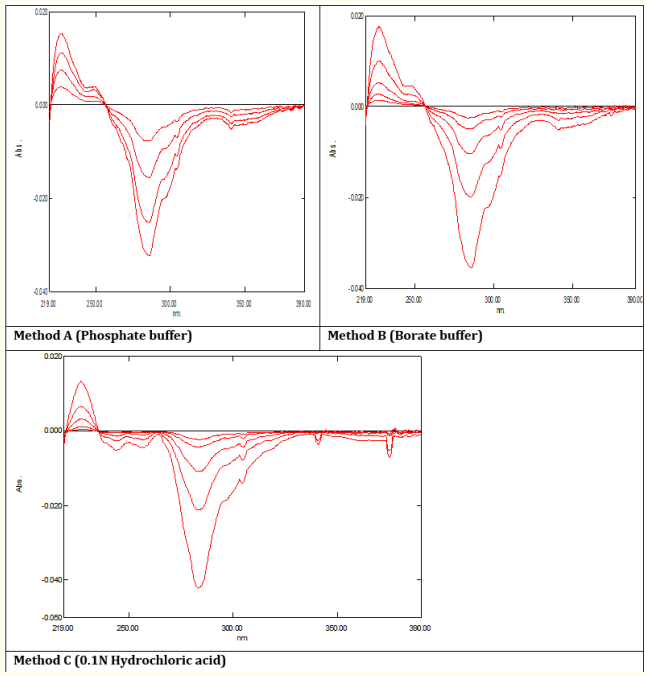

Figure 4: Overlay first order derivative spectrum of Imatinib mesylate.

Table 4: Linearity (First order derivative spectroscopy).

Conc. (µg/ml)	Derivative absorbance (Minima at 284 nm)		
	Method A	Method B	Method C
0.5	-	0.001	0.001
1	0.001	0.002	0.002
2	0.003	0.005	0.004
5	0.008	0.010	0.010
10	0.016	0.018	0.020
15	0.024	-	-
20	0.032	0.034	0.042
25	0.039	-	-
30	0.047	0.050	0.063

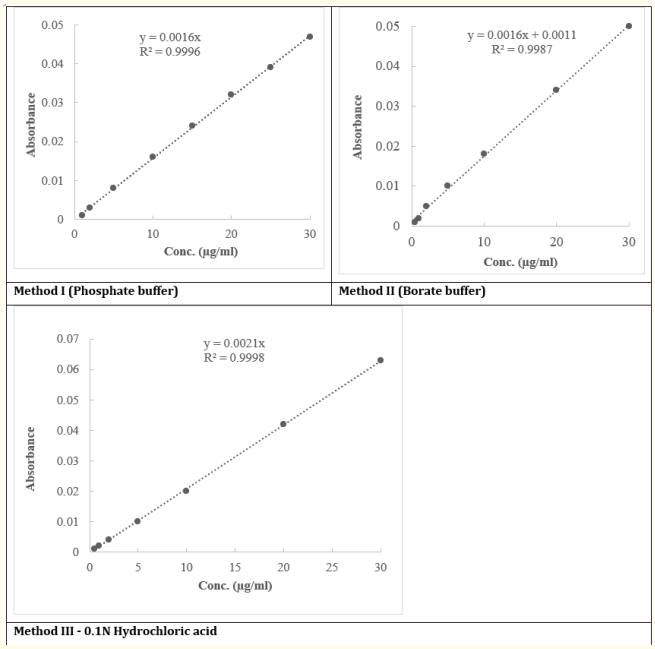

Figure 5: Calibration curves of Imatinib mesylate (First order derivative spectroscopy).

Assay of Imatinib mesylate

Imatinib mesylate tablets of two different formulations were assayed by the above methods and the percentage of purity was found to be 99.89-99.79%.

Conclusion

Imatinib mesylate is an anti-cncer agent. Two different analytical techniques in three different reaent solutions have been developed and validated as per ICH guidelines for the estimation of Imatinib mesylate drug. The methods are precise, accurate and can be applicable for the estimation of Imatinib mesylate in formulations.

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