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Visible Spectrophotometric Determination of Imatinib Mesylate in Bulk Drug and Pharmaceutical Formulations

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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.

Key Words: Imatinib mesylate, Spectrophotometric, Bulk drug, Formulation.

INTRODUCTION

Imatinib is an antineoplastic agent used to treat chronic myelogenous leukemia. Imatinib is a 2-phenylaminopyrimidine derivative that functions as a specific inhibitor of a number of tyrosine kinase enzymes. In chronic myelogenous leukemia, the Philadelphia chromosome leads to a fusion protein of Abl with Bcr (breakpoint cluster region), termed Bcr-Abl. As it is now a continuously active tyrosine kinase, imatinib is used to decrease Bcr-Abl activity. It is chemically 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methanesulfonate. The drug is official in Martindale, The Extra Pharmacopoeia and also included in Merck Index[1,2]. Chemical structure of imatinib is shown in Fig. 1.

Few HPLC methods for quantitative determination of imatinib were reported in the literature. Majority of these HPLC methods were applied in the determination of imatinib and it's metabolites in biological fluids[3-5] and are mainly useful for therapeutic monitoring of the drug. No visible spectrophotometric method for quanti-

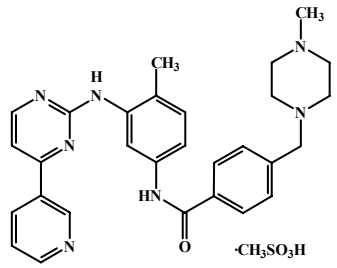

Fig. 1. Chemical structure of imatinib mesylate

tative determination of imatinib in bulk drug samples and formulations was reported. The objective of this research is to develop and validate rapid, economical and sensitive visible spectrophotometric method for quantitative determination of imatinib in bulk drug samples and formulations. Imatinib is having an amino group in the molecular structure making it possible to form the ion-pair complex with acidic dye bromocresol green in acidic buffer solution and undergo oxidative coupling of the drug with 3-methyl-2-benzothiazolinone hydrazone in $FeCl_3$ solution[6-9].

EXPERIMENTAL

Pharmaspec-1700 ultraviolet-visible spectrophotometer (double beam) was used for all spectral measurements. Digisun model DI-707 pH meter was used for all the pH measurements.

All the chemicals used were of analytical grade.

Bromocresol green: 100 mg of bromocresol green was dissolved in 0.72 mL of 0.1 N NaOH and 20 mL of methanol. After solution was affected, sufficient distilled water was added to produce 100 mL.

Phthalate buffer: of pH 2.2 as per Indian Pharmacopoeia.

3-Methyl-2-benzothiazolinone hydrazone (0.1 % w/v): 100 mg of 3-methyl-2-benzothiazolinone hydrazone was dissolved in 50 mL of distilled water.

$FeCl_3$ (0.3 % w/v): 300 mg of ferric chloride hexahydrate was dissolved in 100 mL of distilled water.

Chloroform: AR grade chloroform was used directly.

Procedure

Preparation of standard drug solution: Method A: 100 mg of imatinib was accurately weighed and dissolved in 100 mL of distilled water in a standard volumetric flask to obtain a stock solution of 1 mg/mL.

Mehod B: 10 mL of 1 mg/mL solution was further diluted to 100 mL with distilled water to get 100 µg/mL working standard.

Preparation of sample solution: A quantity of the powder from capsules equivalent to 50 mg of drug was dissolved in 30 mL of distilled water, filtered, volume was made up to 50 mL and analyzed by taking an aliquot from the filtrate and treated as per the procedure for standard.

Method A: Aliquots of standard drug solution (0.25-3.5 mL) were transferred into series of 10 mL graduated test tubes, 2 mL of ferric chloride and 1 mL of MBTH were added to each test tube, mixed well and volume was made upto 10 mL with water. The absorbance of resulting solution was measured at 569 nm against reagent blank prepared simultaneously and a linear graph was obtained. The amount of imatinib present in the sample solution was computed from its calibration curve.

Method B: Aliquots of standard drug solution (0.5-4.0 mL) were added to 5 mL of phthalate buffer of pH 2.2 contained in a separating funnel followed by 0.5 mL of 0.1 % w/v BCG solution.The solution was extracted with chloroform and collected chloroform layer was dried over anhydrous sodium sulfate. Volume was made up to 10 mL. A linear graph was obtained at 417 nm after the waiting period of 15 min, against reagent blank prepared simultaneously. The amount of imatinib present in the sample solution was computed from its calibration curve.

RESULTS AND DISCUSSION

Analytical data and method validation: The optimum conditions were established by varying one parameter at a time and keeping the others fixed and observing the effect on absorbance of chromogen.

The optimum pH required for complexation, effect of dye concentration and efficiency of the solvent to extract the ion pair were studied with respect to maximum sensitivity, colour stability, adherence to Beer's law and other optimum conditions are incorporated in the procedure (Table-1).

TABLE-1
OPTICAL CHARACTERISTICS, PRECISION AND ACCURACY OF THE METHOD

Parameter	Method A	Method B
λ_{max} (nm)	569	417
Beer's law range (µg/mL)	25-350	5-40
Molar extinction coefficient (L mol^{-1} cm^{-1})	0.44×10^4	4.34×10^4
Sandell's sensitivity (µg/cm^2/0.001)	0.38	0.039
Regression equation (y = mx + b) *		
Slope (m)	0.0026	0.0249
Intercept (b)	-0.0073	0.0035
Correlation coefficient (r)	0.9997	0.9998
Precision (% Relative standard deviation)	0.42	0.20

*y = mx + b, where y is the absorbance unit and x is the concentration in µg/mL.

The optical characteristics such as absorption maxima, Beer's law limits, molar absorptivity and Sandell's sensitivity are presented in Table-2.

The regression analysis using the method of least squares was made to evaluate the slope (m), intercept (b) and correlation coefficient (r) obtained from different concentrations and the results are presented in Table-2.The graph showed negligible intercept as described by the regression equation y = mx + b where y is the absorbance and x is the concentration in µg/mL.

TABLE-2
DETERMINATION OF IMATINIB MESYLATE IN FORMULATIONS

Sample	Proposed method	Label claim (mg)	Amount* (mg) found by proposed method	% Recovery**
1	Method A	100	99.98	99.98
	Method B	100	99.75	99.75
2	Method A	100	99.86	99.86
	Method B	100	99.65	99.65

*Average of three determinations, **After spiking the sample.

Commercially available formulations of imatinib were analyzed by the proposed methods and as additional check on the accuracy of the method, recovery experiments were also conducted by spiking known amounts of pure drug in pre-analyzed injection and the recovery was calculated in each of the case using the regression line equation developed under the linearity experiment. The results of recovery experiments were given in the Table-2 for both the methods.The interference studies revealed the common excipients and other additives usually present in pharmaceutical dosage forms did not interfere in the proposed method.

The proposed visible spectrophotometric methods enable quantitative determination of imatinib in bulk drug samples and formulations. Efficient visible spectrophotometric detection at the respective absorption maxima was found to be suitable without any interference from tablet excipients. The calibration curve was linear over a concentration range from 25-350 µg/mL for MBTH and 5.0-40 µg/mL for BCG.The relative standard deviation's (RSD) were less than 1 % and average recovery was above 99.81 %. Analytical results of samples were in accordance with those of standard solution in the same concentrations. The proposed methods are fast, precise, accurate, sensitive and efficient and can be used in routine analysis in quality control laboratories.

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