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QUANTITATIVE DETERMINATION OF BISOPROLOL FUMARATE IN BULK AND PHARMACEUTICAL DOSAGE FORMS BY SPECTROPHOTOMETRY

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ABSTRACT

Two simple, sensitive and accurate spectrophotometric methods have been developed for the determination of bisoprolol fumarate in pure and pharmaceutical formulations. The first method is based on the formation of pink colored chromogen condensation product of bisoprolol fumarate with 2, 6-di-chloroquinone-4-chloroimide (Gibb's reagent) having a λ max at 532 nm. The second method is based on the formation of blue colored complex between bisoprolol fumarate and cobalt thiocyanate (CTC). The colored species formed is the coordination complex of the drug and central metal atom of cobalt thiocyanate, which is extractable into nitrobenzene from aqueous solution, which has absorption maxima at 626 nm. The linearity range of bisoprolol fumarate was found to be 100-500 µg/mL for method-1 and 50 -300 µg/mL for method-2. The developed methods were found to be precise and accurate form the statistical validation of the analytical data. So the proposed methods can be used for the routine analysis of bisoprolol fumarate in tablets.

Key words: Bisoprolol fumarate, Gibb's reagent, Cobalt thiocyanate, Spectrophotometry.

INTRODUCTION

Bisoprolol fumarate USP is a synthetic, beta 1-selective (cardio selective) adre-noceptor blocking agent. The chemical name for bisoprolol fumarate [1]USP is (±)-1 - [4- [[2 - (1-methyl ethoxy) ethoxy] methyl] phenoxy] -3 - [(1- methyl ethyl) amino] -2 - propan- ol

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(E) -2- butanedioate (2 : 1) (salt). It possesses an asymmetric carbon atom in its structure and is provided as a racemic mixture. The S (-) enantiomer is responsible for most of the ß-blocking activity. Its molecular formula is $(C_{13}H_{31}NO_4)_2.C_4H_4O_4$ (Fig. 1). Bisoprolol is a ß-1- selective (cardio selective) adrenoceptor blocking agent without significant membrane stabilizing activity or intrinsic sympathomimetic activity in its therapeutic dosage range. Cardio selectivity is not absolute; however, and at higher doses (≥ 20 mg) bisoprolol fumarate also inhibits beta 2-adrenoceptors, chiefly located in the bronchial and vascular musculature, to retain selectivity. It is, therefore, important to use the lowest effective dose. Literature survey reveals that no visible spectrophotometric methods have been reported for the determination of bisoprolol fumarate. However, a few methods have been reported, which include simultaneous estimation and HPLC methods[2-5].

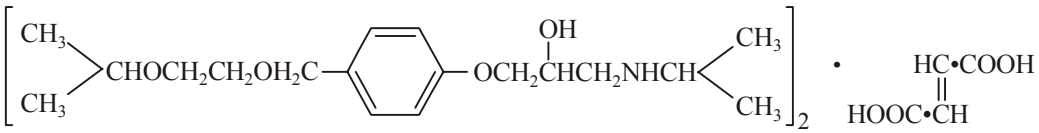

Fig. 1: Structure of bisoprolol fumarate

The present investigation has been undertaken to develop, two simple, accurate, low cost and reliable visible spectrophotometric methods for estimation of bisoprolol fumarate in bulk and its pharmaceutical dosage forms.

EXPERIMENTAL

Spectral and absorbance measurements were recorded by using UV- 1800 double beam UV-Visible spectrophotometer with 10 mm matched quartz cells and software UV Probe -2.31 version. Sample of bisoprolol fumarate was received from M/s Aurobindo Pharmaceuticals, Ltd., Hyderabad, India. All the chemicals used were of analytical grade and distilled water was used through out the work. For the present study, two brands of commercial tablets designated as tablet-1 and tablet-2 containing 5 mg and 2.5 mg of bisoprolol fumarate, respectively were procured from the local drug store.

Reagents and chemicals

2,6–Dichloroquinone-4-chloroimide, 40 mg of Gibb's reagent was accurately weighed and dissolved in 100 mL of isopropanol. Cobalt thiocyanate solution was prepared by dissolving 7.25 g of cobalt nitrate and 3.8 g of ammonium thiocyanate in 100 mL of distilled water. Buffer solution (pH 2.0) was prepared by mixing 25 mL of potassium chloride (0.2 M) and 13 mL of hydrochloric acid (0.2 M) and made up to 100 mL with distilled water and pH was adjusted to 2.0. Analytical grade of nitrobenzene was used.

Preparation of standard drug solution

100 mg of bisoprolol fumarate was accurately weighed and transferred to a 100 mL volumetric flask. The drug was dissolved with 10 mL of distilled water and the volume was made upto 100 mL with distilled water (1 mg/mL).

Recommended procedure

Method-1: Aliquots of standard bisoprolol fumarate solution (1.0-5.0 mL of 1 mg/mL) were transferred into a series of 10 mL volumetric flasks and heated on a water bath for 5 min. Then 5.0 mL of Gibb's reagent was added to each flask and the solution in each flask was made up to 10 mL with isopropanol. The absorbance of all the standards were measured at 532 nm against the reagent blank prepared in a similar manner.

Method-2: Aliquots of standard bisoprolol fumarate solution (0.5 – 3.0 mL of 1 mg/ mL) were transferred into a series of 60 mL separating funnels. Then 2.0 mL of pH 2.0 buffer solution and 3.5 mL of cobalt thiocyanate solution were added and the total volume of aqueous phase in each funnel was adjusted to 10 mL with distilled water. To each separating funnel, 10 mL of nitrobenzene was added and the contents were shaken for 2 min. The two phases were allowed to separate and the absorbance of the separated nitrobenzene was measured at 626 nm against the reagent blank. The colored species was stable for 90 min. (Table 1).

Table 1: Optimum conditions and results of the proposed methods for the determination of bisoprolol fumarate

Reagent	Method-1	Method-2
Drug solution taken (μg/mL)	100-500	50-300
Heating time (min)	5	---
Volume of pH 2.0 buffer solution (mL)	---	2
Volume of reagent employed (mL)	5.0	3.5
λ_{max} (nm)	532	626

Analysis of tablets

Twenty tablets were weighed and ground to fine powder. The tablet powder equivalent to 50 mg of drug was weighed accurately and transferred into a 50 mL volumetric flask and dissolved in about 40 mL distilled water. The solution was filtered through Whatmann filter paper. The filter paper was washed with distilled water. Then the washings were added to the

filtrate and the final volume was made up to 50 mL with distilled water. The solution was assayed as under the assay procedure by method-1 and method-2. The amount of bisoprolol fumarate was computed using the equation referring to the calibration curve.

Recovery studies

Recovery studies were carried out by adding known amount of pure drug to previously analyzed pharmaceutical preparations and the mixtures were analyzed by the proposed methods.

RESULTS AND DISCUSSION

Method-1: The formation of the colored species in this method is due to the formation of condensation product of bisoprolol fumarate with 2, 6-dichloroquinone-4-chloroimide (Gibb's reagent). The optimum conditions were fixed based on the study of the effects of various parameters, such as volume of the Gibb's reagent solution, temperature and time for maximum color development, solvent for final dilution and the stability of the colored species after the final dilution.

Method-2: The blue colored complex formed between bisoprolol fumarate and cobalt thiocyanate can be attributed to the presence of secondary nitrogen in bisoprolol fumarate. The reaction is based on the formation of coordination complex between the drug (electron donor) and the central atom of cobalt thiocyanate. In order to establish optimum sensitivity of the complex, various parameters such as, type of buffer, shaking time, volume of cobalt thiocyanate, stability of the colored complex formed have been varied for a series of solution keeping the other parameters fixed.

The optical characteristics such as Beer's law limit, molar extinction coefficient, Sandell's sensitivity and regression characteristics of the proposed methods are presented in Table 2. Percentage relative standard deviation (calculated from six determinations) and percentage range of error (0.05 and 0.01 confidence limits) for the proposed methods are also given in Table 2. Commercial formulations (tablets) containing bisoprolol fumarate were successfully analyzed by the proposed methods. The values obtained by the proposed methods and reference method were compared statistically by means of F and T-tests and they did not differ significantly at the 95% confidence level. Recovery studies were carried out by adding a fixed amount of the drug to the pre-analyzed formulations and the results are presented in Table 3. The percentage recovery obtained indicates non-interference from excipients used in the formulations.

Table 2: Optical characteristics and precision of the proposed methods for bisoprolol fumarate

Parameters	Method	
	Method-1	**Method-2**
λ_{max} (nm)	532	626
Beer' Law Limit (µg/mL)	100-500	50-300
Sandell's sensitivity (mcg/cm^2/0.001A.U)	0.4662	0.320
Molar absorptivity (L mol^{-1} cm^{-1})	0.949×10^4	0.0137×10^6
Correlation coefficient (r^2)	0.999	0.998
Regression equation (y = b + ax)**		
Slope (a)	0.00209	0.0021
Intercept (b)	0.0080	0.1422
Range of errors*	0.5665	0.4724
Confidence limit with 0.05 level		
Confidence limit with 0.01 level	0.8381	0.6997
% Relative Standard Deviation*	0.6775	0.5656

**y = b + ax

Where, y is absorbance and x is concentration

* Average of six determinations

Table 3: Assay and recovery of bisoprolol fumarate in pharmaceutical formulations

Pharm. formulations	Labeled amount found (mg)	Amount found in[a] (mg) using proposed methods ± S.D		Found by reference method[c] ± S.D	% Recovery by proposed methods[b] ± S.D	
		Method-1	**Method-2**		**Method-1**	**Method-2**
Tablet 1	5.0	5.0 ± 0.0126 F=0.3278 T=0.6554	4.998 ± 0.0240 T=0.8004 F=0.4502	4.992 ± 0.0344	100.00 ± 0.132	99.96 ± 0.019
Tablet 2	2.5	2.495 ± 0.017 F=0.7599 T=0.8990	2.496 ± 0.0149 F=0.5540 T=1.0	2.495 ± 0.0170	99.80 ± 0.261	99.84 ± 0.174

Cont…

[a]Average ± standard deviation of eight determinations, the F and T-values refer to comparison of proposed method with reference method. Theoretical values at 95% confidence limits T =2.365 and F = 4.88.

[b]Recovery of 5.0 mg added to the pre-analyzed pharmaceutical formulations (average of three determinations).

[c]U.V. method using 0.1 N sodium hydroxide as solvent and λ_{max} at 224 nm.

CONCLUSION

The reliability and suitability of the methods could be seen from the recovery values which are satisfactory. Further, there is no interference due the common exciepients.The developed methods are simple, precise, rapid, accurate, reliable, reproducible and cost effective. Thus, the proposed methods can be used successfully for routine analysis of bisoprolol fumarate in bulk and pharmaceutical dosage forms.

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REFERENCES

1. The United States Pharmacopoeia, The USP 24th ED.; Easton. R and McNally: Tounton, MA (2000).
2. R. Sahu and B. Vandana Patel, Indian Pharmaceut. Assoc., **68**, 764 (2006).
3. N. H. Vadia, R. Sahu and B. V. Patel, The Indian Pharmacist., **6,** 81 (2007).
4. A. Atul Shiredkar, R. Thorve Rajesh and J. Surana Sanjay, Pak J. Pharm. Sci., **21,** 366 (2008).
5. Saleem Shaikh, O. A. Thusleem, M. S. Muneera, Javeed Akmal, V. K. Anand, and K. Ruckmani, J. Pharm. Biomed Anal., **48,** 1055 (2008).

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