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Development of Acid–Base Titrimetric Method for Determination of Bisoprolol Fumarate in Raw Material and Tablet Dosage Form

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Abstract

A simple acid –base titrimetric method has been developed for determination of bisoprolol fumarate in pure and tablet dosage form by the reaction of previously neutralized alcoholic solution of the drug with an aqueous solution of sodium hydroxide in 1 : 2 molar ratio, respectively, using phenolthalein as visual acid - base indicator. The method was found to be applicable in the range of 10 – 50 mg. All validation parameters were conducted according to the ICH guidelines and the method was found to be accurate and precise with RSD % less than 2. The added excipients didn't interfere in the proposed procedure as confirmed by recovery studies using standard addition technique with the recovery % 97.4 – 100.8 and RSD% 1.9. The results obtained by the developed method were validated statistically by comparing it with those of reference method by applying the t-test and F-test. The developed method can be used for determination of bisoprolol fumarate in pure and tablet dosage form.

Keywords: *Acid-base titration, Bisoprolol fumarate, excipients, recovery %*

1. Introduction

Bisoprolol is a frequently prescribed medication used in the treatment of cardiovascular disorder [1]. It's a selective type 1 ß-adrenergic receptor blocker [2]. Chemically its (±)-1-{p-[(2-isopropoxyethoxy) methyl] phenoxy}-3-isopropyl-amino-2-propanol hemifumarate [3]. Several analytical method have been reported for determination of bisoprolol fumarate in pharmaceutical preparation; these including high performance liquid chromatographic method [4][5]–[7]. Various spectrophotometric method have been developed [1]–[3], [8], [9]. Also electrochemical methods were found in the literature [11]. Potentiometric non-aqueous acid-base titration is the official method for determination of bisoprolol in both raw material and tablet dosage form in the BP and HPLC method is the official one in USP pharmacopeia [12].

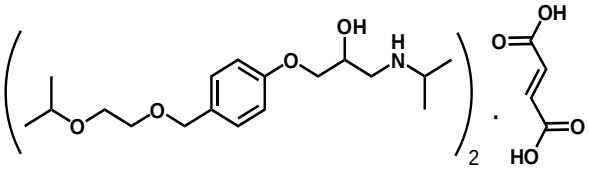

Fig.1: The chemical structure of bisoprolol fumarate

2. Materials and methods

2.1 Materials

Bisoprolol fumarate working standard was kindly gifted from Amipharma laboratories, sodium hydroxide {SDFCL, India}, ethanol 80 % {Khartoum bahri - Sudan}, potassium hydrogen phthalate {E. Merck, India}, perchloric acid { Chem-Lab, Belgium}, glacial acetic acid {Alpha Chemika, India}, acetic acid anhydride {Chem-Lab, Belgium}, phenolphthalein indicator and purified distilled water.

2.2 Methods

2.2.1 Preparation of the reagents

2.2.1.1 Preparation of 0.1 M sodium hydroxide

A solution of sodium hydroxide was prepared by transferring 210 mg of NaOH to 500 mL volumetric flask and the volume was adjusted to the mark with distilled water.

2.2.1.2 Preparation of Potassium hydrogen phthalate (KHP)

204 mg of potassium hydrogen phthalate was transferred to 100 mL volumetric flask then dissolved with distilled

water and the volume was completed to the mark with the same solvent.

2.2.1.3 Preparation of phenolphthalein (ph-ph) indicator

50 mg of ph-ph powder was taken and dissolved in 50 mL of absolute ethanol then the volume was completed to 100 mL with distilled water.

2.2.1.4 Preparation of crystal violet indicator

500 mg of crystal violet was dissolved in 10 mL of glacial acetic acid and transferred to 100 mL volumetric flask then the volume was completed to the mark by using glacial acetic acid.

2.2.3 Standardization of 0.01M Sodium hydroxide

The primary standard of potassium hydrogen phthalate was titrated against the prepared solution of sodium hydroxide using Ph-Ph as indicator then the factor was calculated.

2.2.3 Standardization of 0.01M of perchloric acid

10.22 mg of potassium hydrogen phthalate was dissolved in enough volume of glacial acetic acid then titrated with 0.01M perchloric acid using crystal violet as indicator and the factor was calculated.

2.2.4 Titration

An accurately weighed amount of bisoprolol fumarate was dissolved in sufficient volume of previously neutralized ethanol, two drops of ph-ph indicator were added and titration was carried out against 0.01M NaOH to the pink color end point.

2.2.5 Tablet assay by the proposed method

Twenty tablets of Cardex® (10 mg) were weighed accurately and ground into a fine powder. Powder equivalent to 20 mg of bisoprolol fumatare was weighed and transferred into a 100 mL Erlenmeyer flask and dissolved in sufficient volume of ethanol, ph-ph indicator was added and the titration was conducted against 0.01M NaOH until the color change from colorless to pink color. Blank determination was carried out at the same time.

2.2.6 Tablet assay by the official non–aqueous titration method

Twenty tablets of Cardex® (10 mg) were weighed accurately and ground into a fine powder. Powder equivalent to 10 mg of bisoprolol fumatare was weighed and transferred into a 100 mL Erlenmeyer flask and dissolved in sufficient volume of glacial acetic acid, crystal violet indicator was added and the titration was conducted against 0.01M acetous perchloric acid until the color change to yellowish green at the end point.

2.2.7 Method validation

The method was validated according to ICH guidelines in term of linearity, accuracy, precision, robustness and ruggedness.

3. Results and discussion

Bisoprolol fumarate is an invaluable medication used in various cardiovascular illnesses. There are many local factories which produce it so we aimed to develop a simple analytical method for determination of BF in bulk and tablet dosage form. Based on a revision of the literature, most of the analytical procedures of bisoprolol quantification are based on RP-HPLC methods and spectrophotometric methods, most of them are colorimetric methods, which are tedious, expensive, utilizing different coloring reagents and toxic organic solvents making them not suitable for routine analysis. The official method used for determination of BF is non-aqueous acid-base titration, a method suffering from different drawbacks. The most important drawbacks include: using of toxic and expensive organic solvents and the difficulties of end point determination. So, a simple titrimetric method using less toxic and cheaper solvents is urgently required. The proposed method is based on the titration of ethanolic solution of the drug against 0.01 M NaOH. The stoichiometry of the reaction is 1:2 (Drug : NaOH) ratio and the titre value was found to be 3.835 mg of the drug equivalent to 1 mL of 0.01 M NaOH.

The developed method was validated according to ICH guidelines. The linearity of the method was established by least-square regression analysis of the calibration curve. Five weights of BF (10, 20, 30, 40, 50 mg) were taken and dissolved each one in 10 ml of ethanol 80% then titrated with 0.01M NaOH by using Ph-Ph indicator calibration curve is constructed **Fig. 2** with R^2 0.998 indicate good linearity.

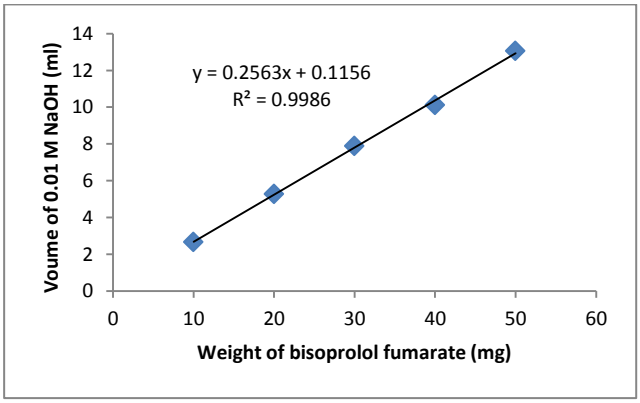

Fig. 2: Standard calibration curve of bisoprolol fumarate working standard

Regarding precision, the reproducibility of the proposed method was determined by performing the analysis at different intervals at the same day (intraday precision) and at three different days (inter-day precision), the results were expressed as RSD % as shown in table 1 and 2.

Table 1: Repeatability of the method

Replicate NO	Content%	
1	101.4	
2	99.6	
3	99.6	**Mean** = 99.6
4	99.6	**SD** = 1.138
5	99.6	**RSD**% = 1.14
6	97.8	

Table 2: Inter day precision of the method

	Mean	SD	RSD%
Level 1	101.68	1.237	1.238
Level 2	98.48	1.206	1.225
Level 3	99.48	1.273	1.42

To confirm the accuracy of the method, recovery study was carried out by using standard addition method at three levels (50, 100, and 150 %) then the recovery % was calculated and the results were presented in table 3 and were found within the accepted limit (95-105%) which confirms that there is no interference from the common excipients present in BF tablet. To study the ruggedness of the proposed method, table 4 showed the results of different analysts and that obtained by changing the burettes. The described method is considered rugged as the RSD% in both situations was found less than 2.

Table 3: Standard addition method

Level	Amount added (mg)	Volume (mL)	Amount recovered (mg)	Recovery %	Mean SD and RSD%
		3.77	14.61	97.41	Mean =
Level 1 (50%)	15	3.77	14.61	97.41	97.41%
		3.77	14.61	97.41	SD = 0
					RSD% = 0
		7.8	29.88	99.61	Mean =
Level 2 (100%)	30	7.9	30.26	100.89	99.19%
		7.6	29.12	97.06	SD = 1.97
					RSD = 1.98
		11.6	45.27	100.61	Mean =
Level 3 (150%)	45	11.5	44.88	99.73	100.88%
		11.8	46.04	102.3	SD = 1.31
					RSD% = 1.29

Table 4: Ruggedness of the method

Analyst	Content %		Burette	Content %	
1	104.09	Mean = 104.09	**1**	98.75	**Mean** =99.45
2	104.09	SD = 0	**2**	99.71	**SD** = 0.61
3	104.09	RSD% = 0	**3**	99.90	**RSD% =** 0.62

The proposed method was compared with the official non-aqueous titration method and the result was evaluated statistically at confidence level of 95%. The t-test was applied and the t- calculated was found less than t- tabulated which confirm the accuracy of the method. On the other hand, the F-test was applied and the F-calculated was found less than F-tabulated further confirm that; there are no significant differences in the precision of the two methods.

Table 5: Comparison between the proposed method and official method

Sample	Content % by the proposed method	Content % by the official method	
1	99.6	99.2	t-calculated **=** 0.331
2	99.6	99.03	t- tabulated = 2.306
3	99.6	99.03	F- calculated = 1.531
4	99.6	100.9	F-tabulated = 3.44
5	101.4	100.9	
Mean ± SD	99.96±0.80	99.81±0.99	

Conclusions

The developed acid-base titrimetric method was linear, precise, accurate, rugged and simple method compare with the official methods which either require expensive instruments or highly skilled personnel. The developed method can be used for routine analysis of bisoprolol fumarate in bulk and tablet dosage form; furthermore, we can utilize this approach for determination of drugs available as fumarate salts.

Acknowledgement

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