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ORIGINAL ARTICLE

Optimized and validated spectrophotometric methods for the determination of amiodarone hydrochloride in commercial dosage forms using *N*-bromosuccinimide and bromothymol blue

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N-bromosuccinimide;
Bromothymol blue;
Commercial dosage forms

Abstract Two optimized and validated spectrophotometric methods have been developed for the determination of amiodarone hydrochloride in commercial dosage forms. Method A is based on the reaction of tertiary amino group of the drug with *N*-bromosuccinimide in methanol–acetone medium resulting in the formation of a yellow colored product, which absorbed maximally at 353 nm. Method B involves the formation of a colored chloroform extractable ion-pair complex of the drug with bromothymol blue at pH 2.32 absorbing maximally at 400 nm. Beer's law is obeyed in the concentration ranges 50–600 and 2–55 μg mL^{-1} with molar absorptivity of 1.58×10^2 and 1.50×10^4 L mol^{-1} cm^{-1} for methods A and B, respectively. The regression analysis yields the calibration equations: $A = 4.012 \times 10^{-4} + 1.16 \times 10^{-3}$ C and $A = 9.612 \times 10^{-4} + 2.198 \times 10^{-2}$ C for methods A and B, respectively. The application of the proposed methods to commercial dosage forms is presented.

1. Introduction

Amiodarone hydrochloride is a potent III antiarrhythmic drug (Zipes et al., 1984) and is chemically known as 2-butyl-3-benzofuranyl 4-[2-(diethyl amino) ethoxy]-3,5-diidophenyl methanone hydrochloride. It is used to treat ventricular and supraventricular arrhythmias, especially when they are resistant to other conventional antiarrhythmic drugs (Levy, 1988; Mason, 1987). The drug is officially listed in The British

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Pharmacopoeia (2009) and describes the potentiometric titration for the assay of amiodarone HCl.

The analytical techniques that have been utilized for the quantification of this drug in biological fluids and pharmaceutical formulations include high performance liquid chromatography (Rodrigues et al., 2013; Al Riyami, 2010; Khan et al., 2005; Cervelli et al., 1981; Brien et al., 1983; Flanagan et al., 1985; Hug et al., 1991; Vio and Mamoto, 1998), high performance thin layer chromatography (Yang and Fang, 1995), liquid chromatography (Gupta and Connelly, 1984; Geoffriau et al., 1992), infrared spectroscopy (Jensen et al., 1988), Raman spectroscopy (Orkoula et al., 2007), fluorescence spectroscopy (Mohamed et al., 1998), enzyme linked immunosorbent assay and electrochemical methods (Saita et al., 2002; Ball et al., 1996). The literature survey revealed that only few spectrophotometric methods are available for its quantification. A spectrophotometric method was presented for the assay of amiodarone based on reaction of the drug with citric acid–acetic anhydride (Rao and Sastry, 2002) reagent to provide a bluish-violet color having an absorption maximum at 580 nm. However, Beer's law was obeyed over the concentration range 2–12 μg mL^{-1} but required 45 min to complete the analysis. Amiodarone was found to form insoluble molecular complexes with iodine, ammonium molybdate (AM) or phosphomolybdic acid (PMA) (Rao et al., 2002) under acid conditions and spectrophotometric methods were developed based on the color formation with either unreacted precipitant in the filtrate (I_2) or released precipitant form the precipitate (AM or PMA) with chromogenic reagents. However, these methods are tedious to perform and time consuming. Extractive spectrophotometric methods have also been developed based on chloroform extractable ion-association complex (Rao et al., 2001) of the drug with tropaeolin 00, tropaeolin 000, or wool fast blue. Amiodarone was also determined spectrophotometrically using the charge transfer complexation reaction of the drug with p-chloronilic acid and 2,3-dichloro 5,6-dicyano 1,4-benzoquinone (Rahman et al., 2004), and chloranil and iodine (Ebeid et al., 1998). Spectrophotometry is the technique of choice even today due to its low cost, inherent simplicity and adaptability (Czegan and Hoover, 2012). It has wide application in the quantitative analysis of pharmaceutical drugs in clinical and pharmaceutical laboratories.

The present paper describes two simple and accurate spectrophotometric methods for the assay of amiodarone hydrochloride in bulk and commercial dosage forms. Method A is based on bromination of drug with *N*-bromosuccinimide whereas method B utilizes chloroform extractable ion-association complex of drug with bromothymol blue (BTB). The reaction conditions of the proposed methods are thoroughly studied, optimized and validated as per the International Conference on Harmonisation (ICH, 1995).

2. Experimental

2.1. Apparatus

The absorbance measurements were made on a Spectronic $20D^+$ Spectrophotometer (Milton Roy Company, USA) with 1 cm matched glass cells. A water bath shaker (Narang Scientific Works Pvt. Limited, New Delhi, India) was used to control the temperature.

2.2. Reagents and marketed tablets

Amiodarone hydrochloride was kindly provided by Troikaa Pharmaceutical Ltd. India and was used as received. Commercial dosage forms of amiodarone hydrochloride such as Duron (Samarth Pharma Pvt. Ltd., India), Cardarone (Sanofi Synthelabo (India) Ltd.) and Amiodar (Cardicare, India) were purchased from local drug stores, labeled to contain 100 mg amiodarone hydrochloride per tablet.

- *N-bromosuccinimide* (1.12×10^{-1} M; S.d. fine Chem. Ltd., India) solution was prepared in acetone.
- Bromothymol blue (4.01×10^{-4} M, Loba chemie Pvt. Ltd., India) solution was prepared in distilled water.
- Sodium acetate-hydrochloric acid buffer of pH 2.32 was prepared by mixing 50 mL of 1.0 M sodium acetate solution with 51 mL of 1.0 M HCl and diluted to 250 mL with distilled water (Britton, 1942).

2.3. Test solutions

- Amiodarone hydrochloride (1 mg mL^{-1}) solution was prepared in methanol for method A.
- Amiodarone hydrochloride (0.5 mg mL^{-1}) solution was prepared in chloroform for method B.

2.4. Proposed procedures for the determination of amiodarone hydrochloride

2.4.1. Method A

Aliquots of standard solution of amiodarone hydrochloride (1 mg mL^{-1}) equivalent to 0.25–3.0 mg were transferred into a series of boiling tubes. To each tube, 1.7 mL of 1.12×10^{-1} M *N*-bromosuccinimide was added and the contents were heated on a water bath at 40 ± 1 °C for 10 min. After cooling at room temperature, the contents were transferred to a 5 mL volumetric flask and the volume was completed up to the mark with methanol. The absorbance of the colored product was measured at λ_{max} = 353 nm against the reagent blank prepared similarly except amiodarone. The calibration curve was plotted and regression equation was developed.

2.4.2. Method B

Into a series of 50 mL separating funnels, 5 mL of buffer solution of pH 2.32 and 5 mL of BTB were placed. An appropriate volume (0.04–1.1 mL) of amiodarone hydrochloride (0.5 mg mL^{-1}) was added to each funnel and mixed well. The funnels were shaken vigorously with 10 mL chloroform for 2 min, and then allowed to stand for clear separation of two phases. The absorbance of the organic phase was measured at λ_{max} = 400 nm against the reagent blank prepared simultaneously.

2.5. Determination of amiodarone hydrochloride in commercial dosage forms

Ten tablets were powdered and mixed thoroughly. For method A, an amount of the tablet powder equivalent to 100 mg of amiodarone hydrochloride was weighed accurately and extracted into 50 mL methanol with shaking. Filtration through Whatmann No. 42 filter paper was performed. The filtrate was

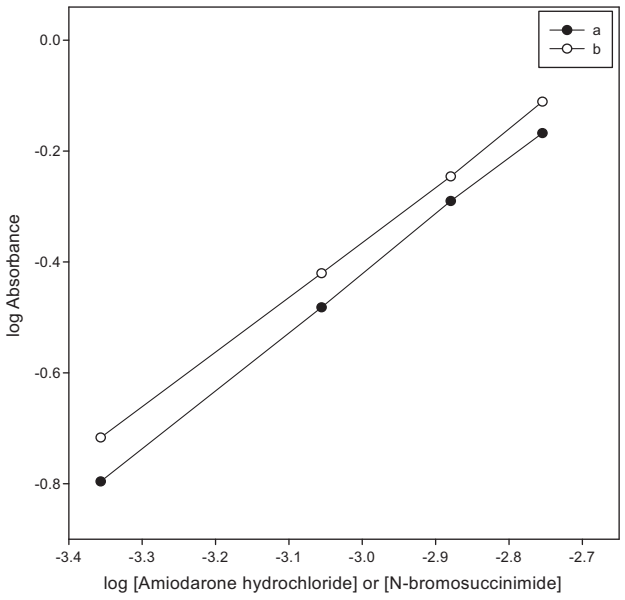


Figure 1 Bent and French stoichiometric plot of (a) amiodarone hydrochloride and (b) *N*-bromosuccinimide for method A.

diluted to 100 mL with methanol. For method B, an amount of the tablet powder equivalent to 100 mg amiodarone hydrochloride was stirred well with chloroform and filtered through Whatmann No. 42 filter paper. The filtrate and washings were diluted to volume in a 100 mL volumetric flask. The assay was completed following the proposed procedures.

2.6. Evaluation of bias

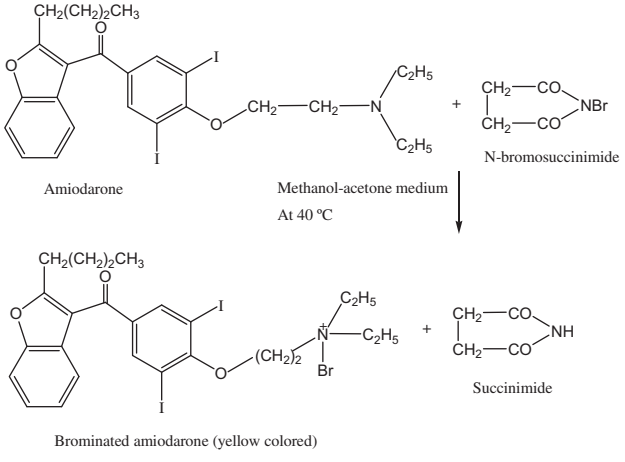
The bias has been evaluated by means of point and interval hypothesis tests (Hartmann et al., 1995; Canada Health Protection Branch, 1992). In interval hypothesis the proposed method is accepted when the true mean is within ± 2% of that of the true reference method (method 1), i.e.,

$$-0.02\,\mu_1 < (\mu_2 - \mu_1) < 0.02\,\mu_1$$

The above equation can also be written as:

$$0.98 < \mu_2/\mu_1 < 1.02$$

which can be generalized to



Scheme I Reaction sequence of method A.

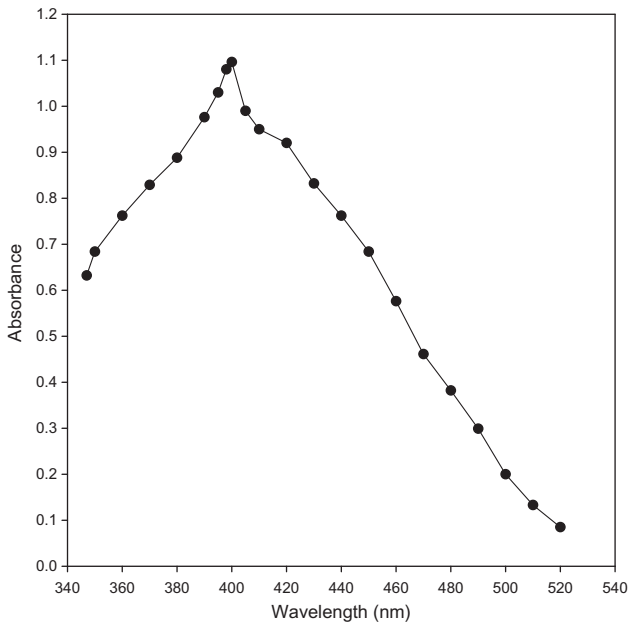


Figure 2 Absorption spectrum of amiodarone hydrochloride ($50.0\ \mu g\ mL^{-1}$) + 3.5 mL of 4.01×10^{-4} M BTB + 5.0 mL of sodium acetate–HCl buffer solution of pH 2.32 for method B. The solution is extracted in 10 mL chloroform for absorption spectrum of the ion-pair complex.

$$\theta_L < \mu_2/\mu_1 < \theta_u$$

where θ_L and θ_U are lower and upper acceptance limits, respectively. The limits of this confidence interval can be calculated as the two roots of the following quadratic equation.

$$\theta^2\left(\overline{x_1^2} - S_p^2 t_{tab}^2/n_1\right) - 2\theta\overline{x_1 x_2} + \left(\overline{x_2^2} - S_p^2 t_{tab}^2/n_2\right) = 0$$

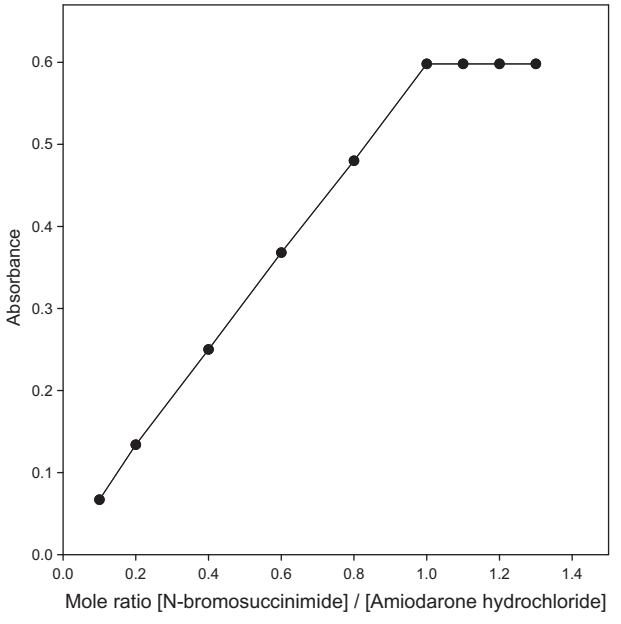


Figure 3 Mole ratio plot for stoichiometric ratio between amiodarone hydrochloride and *N*-bromosuccinimide (1.10×10^{-2} M each) for method A.

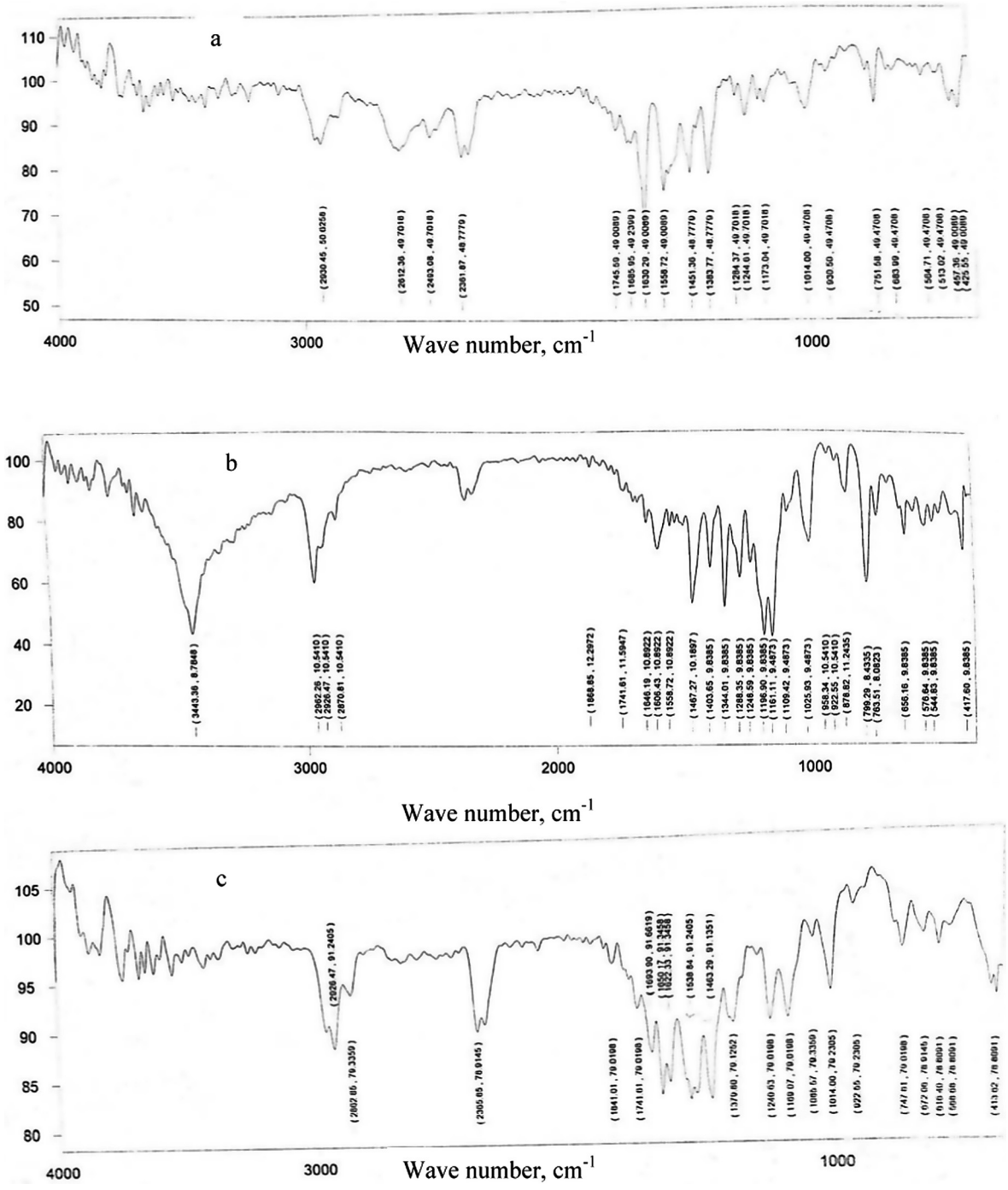


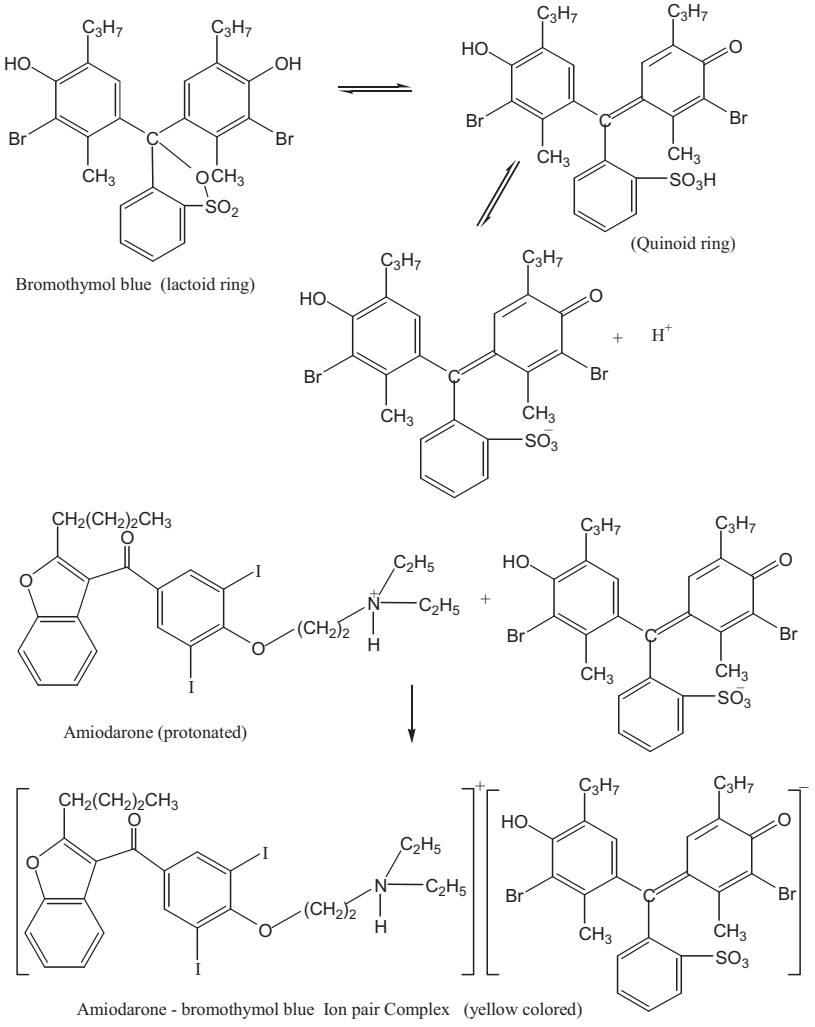
Figure 4 FTIR spectra of (a) amiodarone hydrochloride (b) bromothymol blue and (c) amiodarone–bromothymol blue complex.

where S_p is the pooled standard deviation and t_{tab} is the student's t-value at the given confidence level.

3. Results and discussion

N-bromosuccinimide is an extremely useful and a versatile reagent (Barakat and Mousa, 1952). Its unique brominating ability has been attributed to its almost non-polar *N*-bromine bond, as well as the favorable geometric arrangement, which exists between the *N*-bromine and carbonyl function. It has been reported (Dunstan and Henbest, 1957) that tertiary amine reacts with *N*-bromosuccinimide resulting in the formation of colored intermediate, which on hydrolysis yields aldehydes and brominated secondary amine whereas *N*-bromosuccinimide is irreversibly reduced to succinimide. This can be expressed as:

$$(R-CH_2)_3N + BrN(COCH_2)_2 \rightarrow \text{Colored Intermediate} \xrightarrow{H_2O} RCHO + (R-CH_2)_2NH_2Br + HN(COCH_2)_2$$



Scheme II Reaction sequence of method B.

Similarly, in the present study, the amiodarone contains a tertiary amino group, which reacts quantitatively with *N*-bromosuccinimide in methanol–acetone medium resulting in the formation of a colored product absorbing maximally at 353 nm. The stoichiometry of the reaction was studied adopting the limiting logarithmic method (Bent and French, 1941). The absorbance of the reaction product was alternatively measured in the presence of excess of *N*-bromosuccinimide and amiodarone hydrochloride. A plot of log absorbance vs. log [*N*-bromosuccinimide] and log [amiodarone hydrochloride] gave straight lines; the values of the slopes were 1.05 and 1.00, respectively (Fig. 1). It is concluded that the reaction proceeds in the ratio of 1:1. Based on the obtained molar reactivity, the reaction pathway is shown in Scheme I.

At pH 2.32, the amino group of amiodarone is protonated while the sulfonic acid group present in BTB is undergoing dissociation. The color of BTB is due to the opening of the lactoid ring and subsequent formation of the quinoid group. It is supposed that the two tautomers are present in equilibrium but due to strong acidic nature of the sulfonic acid group, the quinoid body must predominate. Finally, the protonated amiodarone forms an ion-pair with BTB, which is quantitatively extracted into chloroform. The ion-pair complex absorbed maximally at 400 nm and the reagent blank under similar conditions showed no absorption at the specified wavelength. The absorption spectrum is shown in (Fig. 2). The stoichiometry was established by the mole ratio method (Sawyer et al., 1984). As can be seen from Fig. 3 that the molar ratio of amiodarone to BTB was 1:1. The FTIR spectra of amiodarone hydrochloride, bromothymol blue and amiodarone-bromothymol blue ion pair are shown in Fig. 4a–c. In the FTIR spectrum of amiodarone hydrochloride, stretching vibrations of –C═O, –C–O–C–, N–H^+ and C–N occurred at 1630, 1244, 2365 and 1173 cm^{-1}, respectively (Socrates, 1980). The FTIR spectrum of bromothymol blue exhibited bands at 1196 cm^{-1} and 1025 cm^{-1} which are assigned to –SO_3 group (Silverstein and Webster, 2005). The band appearing at 656 cm^{-1} is due to C–Br stretching vibrations. The FTIR spectrum of the amiodarone–bromothymol blue ion pair complex showed the bands due to the stretching vibrations of –C═O, C–O–C, N–H^+, C–N, SO_3– and C–Br groups, thus confirming the formation of the ion pair complex extractable into chloroform. On the basis of our experimental findings and literature background, the reaction sequence is shown in Scheme II.

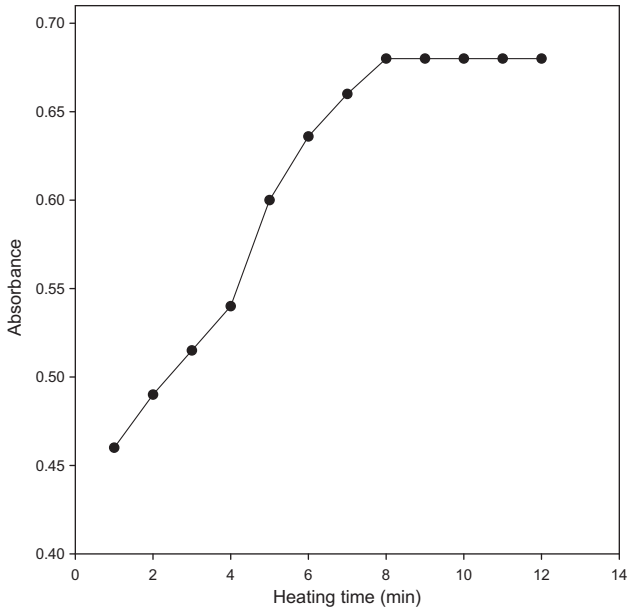


Figure 5 Effect of heating time on the absorbance of color reaction between amiodarone hydrochloride and *N*-bromosuccinimide for method A.

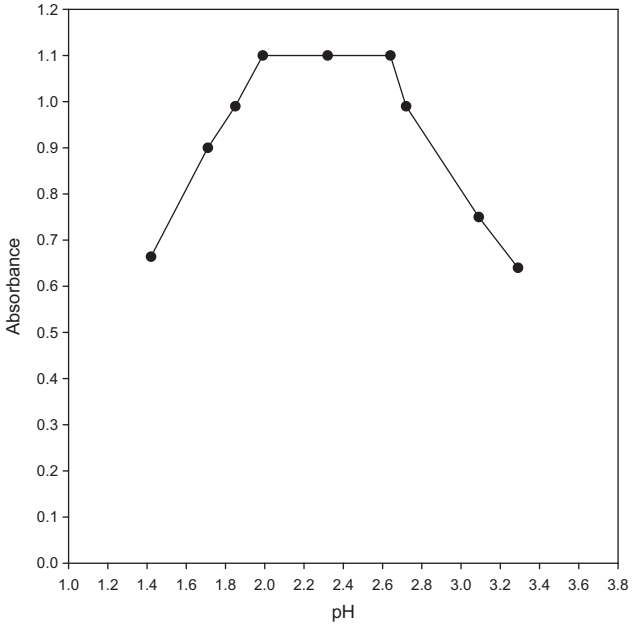


Figure 7 Effect of pH: 50.0 μg mL^{-1} amiodarone hydrochloride + 5.0 mL of sodium acetate–HCl buffer solution of different pH + 3.5 mL of 4.01×10^{-4} M BTB (Method B).

3.1. Optimization of variables

The optimum conditions for the assay procedures (methods A and B) have been established by studying the reactions as a function of heating time, concentration of reagents, pH and nature of solvent.

3.1.1. Method A

3.1.1.1. Effect of heating time. To investigate the optimum heating time for color development, aliquots of amiodarone hydrochloride (3 mg) were transferred into a series of boiling tubes. To each tube, 2 mL of 1.12×10^{-1} M *N*-bromosuccinimide was added followed by 5 mL of methanol. The tubes were placed on a waterbath maintained at 40 ± 1 °C for different time intervals. The results are shown in Fig. 5. As can be seen from Fig. 4 that the maximum absorbance was obtained at 8 min and remained constant up to 12 min. Therefore, 10 min heating time was used throughout the experiment.

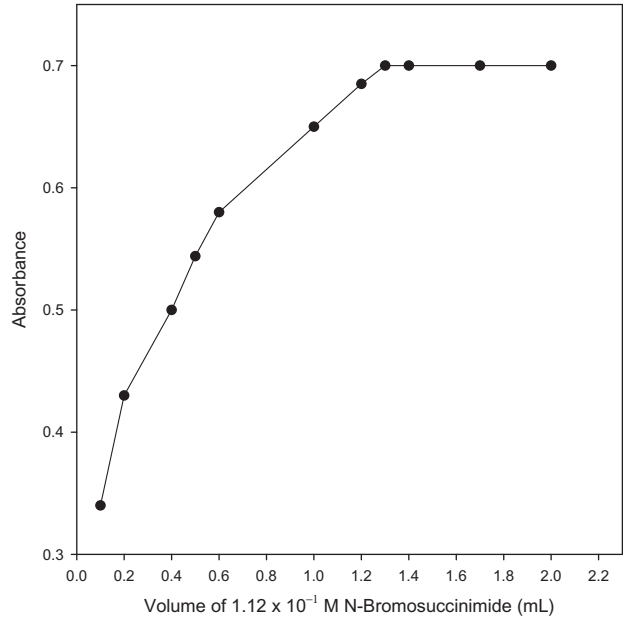


Figure 6 Effect of the volume of 1.12×10^{-1} M *N*-bromosuccinimide on the absorbance of yellow product (600.0 μg mL^{-1} amiodarone hydrochloride).

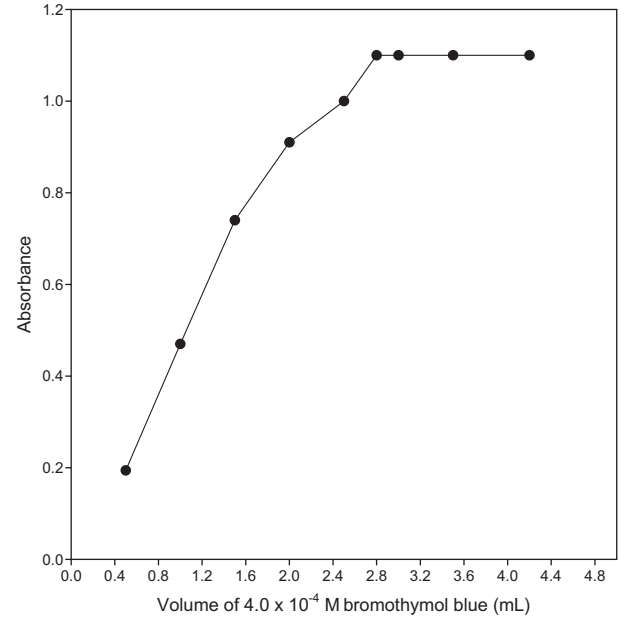


Figure 8 Effect of the volume of 4.01×10^{-4} M BTB on the absorbance of the ion pair complex (50.0 μg mL^{-1} amiodarone hydrochloride; 5.0 mL of buffer solution of pH 2.32).

Table 1 Test of precision of the proposed methods.

Proposed methods	Concentration ($\mu g\ mL^{-1}$)		Recovery	RSD	SAE[b]	CL[c]
	Taken	Found ± SD[a]	(%)	(%)		
Method A						
Intraday assay	160	159.98 ± 0.15	99.99	0.09	0.07	0.18
	360	359.99 ± 0.14	99.99	0.04	0.06	0.17
	560	560.02 ± 0.13	100.00	0.02	0.06	0.16
Interday assay	160	159.99 ± 0.22	100.00	0.14	0.01	0.27
	360	359.96 ± 0.20	99.99	0.06	0.09	0.25
	560	559.98 ± 0.18	100.00	0.03	0.08	0.22
Method B						
Intraday assay	5	5.01 ± 0.08	100.18	1.49	0.03	0.09
	25	25.00 ± 0.06	100.02	0.25	0.03	0.08
	50	49.99 ± 0.07	99.99	0.14	0.03	0.09
Interday assay	5	5.01 ± 0.10	100.18	2.07	0.05	0.13
	25	25.00 ± 0.09	100.03	0.38	0.04	0.12
	50	49.99 ± 0.10	99.99	0.20	0.05	0.13

[a] Mean for five independent analysis.
[b] SAE, standard analytical error.
[c] CL, confidence limit at 95% confidence level and 4 degrees of freedom ($t = 2.776$).

3.1.1.2. Effect of N-bromosuccinimide concentration. The influence of the volume of 1.12×10^{-1} M *N*-bromosuccinimide on the color development was examined in the range of 0.1–2.0 mL. The highest absorbance was obtained with 1.5 mL, which remained unchanged with higher amount of *N*-bromosuccinimide (Fig. 6). Thus, 2.0 mL of the reagent was selected as an optimum value for the determination process.

3.1.2. Method B

3.1.2.1. Effect of the pH. The influence of pH on the ion-pair formation between amiodarone and BTB was studied using a sodium acetate-hydrochloric acid buffer in the pH range of 1.4–3.3 .The results are shown in Fig. 7. It was observed that the maximum and constant absorbance was found between pH 1.99 and 2.64. Thus, a buffer of pH 2.32 was used in further studies.

3.1.2.2. Effect of bromothymol blue concentration. The effect of the volume of 4.01×10^{-4} M BTB was studied in the range of 0.5–5.0 mL. The maximum absorbance was found with 3 mL of BTB; above this volume the absorbance remained unchanged (Fig. 8). Thus, 3.5 mL of BTB was used for the ion-pair formation throughout the experiment.

Table 2 Standard addition technique for the determination of amiodarone hydochloride in dosage forms.

Formulations	Concentration, ($\mu g\ mL^{-1}$)			SAE[b]	CL[c]
	Nominal	Added	Found ± SD[a]		
Method A					
Cardarone 100	80	80	159.93 ± 0.15	0.07	0.19
(Sanofi Synthelabo)	80	160	239.91 ± 0.14	0.06	0.17
Duron 100	80	80	160.02 ± 0.17	0.07	0.21
(Samarth Pharma)	80	160	240.03 ± 0.20	0.09	0.25
Amiodar 100	80	80	160.03 ± 0.13	0.06	0.16
(Cardicare)	80	160	240.03 ± 0.13	0.06	0.16
Method B					
Cardarone 100	15	20	35.03 ± 0.10	0.05	0.13
(Sanofi Synthelabo)	15	40	55.01 ± 0.09	0.04	0.11
Duron 100	15	20	35.01 ± 0.04	0.02	0.05
(Samarth Pharma)	15	40	55.02 ± 0.05	0.02	0.07
Amiodar 100	15	20	35.01 ± 0.05	0.02	0.06
(Cardicare)	15	40	55.02 ± 0.05	0.02	0.07

[a] Mean for five independent analysis.
[b] SAE, standard analytical error.
[c] CL, confidence limit at 95% confidence level and 4 degrees of freedom ($t = 2.776$).

Table 3 Spectrophotometric determination of amiodarone hydrochloride in synthetic mixture samples by proposed methods A and B.

Synthetic samples	Method A			Method B		
	Concentration ($\mu g\ mL^{-1}$)		Recovery	Concentration ($\mu g\ mL^{-1}$)		Recovery
	Taken	Found	(%)	Taken	Found	(%)
[a]1	600.00	600.06	100.01	30.00	29.99	99.66
[b]2	400.00	399.00	99.75	50.00	50.02	100.04

[a] Amiodarone hydrochloride (100 mg) with colloidal silicon dioxide (50 mg), lactose monohydrate (50 mg), magnesium stearate (30 mg), povidone (20 mg), starch (50 mg) and FD & C Red 40 (5 mg).
[b] Amiodarone hydrochloride (50 mg) with colloidal silicon dioxide (50 mg), lactose monohydrate (50 mg), magnesium stearate (20 mg), maize starch (25 mg), povidone (15 mg) and talc (30 mg).

3.1.2.3. Choice of organic solvent and time of shaking. A variety of organic solvents such as benzene, toluene, hexane, chloroform, ethyl acetate, carbon tetrachloride and 1,2-dichloromethane were examined for extraction of the ion-pair. However chloroform was preferred owing to selective extraction of the ion-pair complex from the aqueous solution.

The time of shaking for complete extraction of the ion-pair complex was studied in the range of 0.5–4 min. It was found that the absorbance remained constant over this time period. Thus, 2 min shaking time was used as an optimum value throughout the experiment.

3.2. Linearity, limits of detection and quantitation

Under the optimized experimental conditions, the absorbance-concentration plots were found to be linear over the concentration ranges 50–600 $\mu g\ mL^{-1}$ and 2–55 $\mu g\ mL^{-1}$ of amiodarone hydrochloride with molar absorptivity of 1.58×10^2 and 1.50×10^4 L $mol^{-1}cm^{-1}$ for methods A and B, respectively. The linear regression analysis of calibration data gave the following equations:

$$A = 4.012 \times 10^{-4} + 1.16 \times 10^{-3}C$$

$r = 0.9999$ for method A

Table 4 Applicability of the proposed spectrophotometric method for the determination of amiodarone hydrochloride in commercial dosage forms by the proposed methods and the reference method.

Formulations	Nominal Content ($\mu g\ mL^{-1}$)	Content found ($\mu g\ mL^{-1}$)	RSD (%)	Reference method	
				Content found ($\mu g\ mL^{-1}$)	RSD (%)
Method A					
[a]Cardarone 100 (Sanofi Synthelabo)	600.00	600.06 $\theta_L = 0.986$ $t = 0.022$	0.02 $\theta_u = 1.014$ $F = 1.04$	599.4	0.02
[b]Duron 100 (Samarth Pharma)	600.00	600.06 $\theta_L = 0.991$ $t = 0.033$	0.02 $\theta_u = 1.008$ $F = 1.36$	599.4	0.02
[c]Amiodar 100 (Cardicare)	600.00	600.06 $\theta_L = 0.985$ $t = 0.002$	0.02 $\theta_u = 1.015$ $F = 1.18$	600.06	0.02
Method B					
[a]Cardarone 100 (Sanofi Synthelabo)	50.00	50.00 $\theta_L = 0.988$ $t = 0.012$	0.12 $\theta_u = 1.012$ $F = 1.38$	49.95	0.14
[b]Duron 100 (Samarth Pharma)	50.00	50.04 $\theta_L = 0.987$ $t = 0.189$	0.13 $\theta_u = 1.011$ $F = 1.22$	49.95	0.14
[c]Amiodar 100 (Cardicare)	50.00	50.02 $\theta_L = 0.987$ $t = 0.111$	0.13 $\theta_u = 1.012$ $F = 1.18$	50.00	0.03

[a] Cordorone 100 has the following excipients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, povidone, corn starch and FD and C Red 40.
[b] Duron 100 has the excipients such as: silica colloidal anhydrous, crospovidone lactose monohydrate, magnesium stearate, maize starch, povidone and talc.
[c] The excipients of amiodar 100 are: colloidal silicon dioxide, lactose monohydrate, maize starch, povidone and talc.

$A = 9.612 \times 10^{-4} + 2.198 \times 10^{-2}C$
$r = 0.9999$ for method B

where A is the absorbance, C is the concentration in μg mL^{-1} and r is the correlation coefficient. The values of confidence limit at 95% confidence level for slopes were found to be $1.16 \times 10^{-3} \pm 6.87 \times 10^{-6}$ and $2.198 \times 10^{-2} \pm 4.07 \times 10^{-4}$ whereas for intercepts of calibration lines were $4.012 \times 10^{-4} \pm 2.41 \times 10^{-3}$ and $9.612 \times 10^{-4} \pm 1.33 \times 10^{-3}$ for methods A and B, respectively. The good linearity of the calibration graphs and the negligible scatter of the experimental points were clearly evident from the values of correlation coefficient and variance of calibration lines (3.24×10^{-6} and 1.06×10^{-6} μg mL^{-1} for methods A and B, respectively). Test of significance for intercepts of the regression lines was performed. For this, the values of t- were calculated using the relation $t = a/S$ (Nalimov, 1963) and found to be 0.393 and 1.705 for methods A and B, respectively which did not exceed the tabulated t-value ($t = 2.367$, $v = 7$) at 95% confidence level. It confirmed that the intercepts for the proposed methods are not significantly different from zero.

The limits of detection for methods A and B were calculated and found to be 5.12 and 0.16 μg mL^{-1}, while the limits of quantitation were 15.52 and 0.50 μg mL^{-1}, respectively.

3.3. Accuracy and precision

The within day precision was evaluated through replicate analysis ($n = 5$) of quality control samples: 160, 360 and 560 μg mL^{-1} for method A and 5, 25 and 50 μg mL^{-1} for method B. The percentage recoveries ranged from 99.99 to 100.00 with % RSD from 0.02% to 0.09% and 99.99% to 100.18% with RSD from 0.14% to 1.49% for methods A and B, respectively. The interday precision was also evaluated through replicate analysis of the quality control samples for five consecutive days at the same concentration levels as used in within day precision. The percentage recoveries for methods A and B ranged from 99.99% to 100.00% with RSD from 0.03% to 0.14% and 99.99% to 100.18% with RSD from 0.20% to 2.07%, respectively (Table 1). The results in Table 1 indicate high precision of the proposed methods. The selectivity of the proposed methods was investigated by observing any interference encountered from the excipients of the tablets such as magnesium stearate, talc, lactose, starch and gelatin. It was observed that these excipients did not interfere with the proposed methods.

The standard addition method was applied to check the validity of the proposed methods for the determination of amiodarone hydrochloride in commercial tablets (Table 2). The synthetic mixture samples of amiodarone hydrochloride were prepared and analyzed for % recovery of amiodarone hydrochloride. The results are summarized in Table 3. The percentage recoveries were in the range of 99.66–100.04% for methods A and B. This study has further confirmed that the common excipients present in tablet formulations did not interfere with the assay.

The proposed methods were applied to the determination of amiodarone hydrochloride in commercial tablets such as

Table 5 Comparison of the proposed spectrophotometric methods with existing related techniques for the assay of amiodarone HCl in pharmaceutical formulations.

Reagents	$\lambda_{max,\ nm}$	Molar absorptivity, l mol^{-1} cm^{-1}	Linear dynamic range, μg mL^{-1}	RSD, %	Reference
Spectrophometry: p-chloranilic acid	535	1.42×10^3	10–360	0.11–0.91	Rahman et al. Rahman et al. (2004)
2,3-Dichloro-5,6-dicyanao-1,4-benzoquinone	570	7.50×10^3	2–65	0.16–1.48	Rahman et al. Rahman et al. (2004)
Extractive spectrophometry: Tropaeolin 00	420	–	2.5–15	–	Rao et al. Rao et al. (2001)
Tropaeolin 000	480	–	3–30	–	Rao et al. Rao et al. (2001)
Wool fast blue	580	–	0.75–7.5	–	Rao et al. Rao et al. (2001)
Cobalt thiocyanate	620	–	25–300	–	Rao et al. Rao et al. (2001)
Fluorimetry: Native fluorescence in 0.1 N sulfuric acid medium			40–200		Mohamed et al. Mohamed et al. (1998)
HPLC: Mobile phase: Buffer solution of pH 5: methanol: acetonitrile (3:3:4, v/v/v)	UV detector 240	–	5–15	–	Al Riyami (2010)
Capillary electrophoresis	UV detector 240	–	0.004–0.1	–	Zhang and Thormann Zhang and Thormann (1996)
Spectrophometry: method A (*N*-bromosuccimide)	353	1.58×10^2	10–360	0.03–0.14	This work
Extractive spectrophometry: method B (bromothymol blue)	400	1.50×10^4	2–55	0.2–2.07	This work

Duron, Amiodar and Cardarone. The same batch of commercial dosage forms was also analyzed by the reference method (Rahman et al., 2004). The results of the proposed methods were compared with those obtained by the reference method. Statistical analysis of the results using Student's *t*-test, variance ratio *F*-test and interval hypothesis test (Christian, 1994) revealed no significant difference between the proposed method (A or B) and the reference method at 95% confidence level regarding accuracy and precision. The results are summarized in Table 4. When the proposed methods are compared with other methods for determining amiodarone hydrochloride in pharmaceuticals (Table 5) it can be seen that their sensitivity is higher than most of the compared methods. Only methods with sample preconcentration (Al Riyami, 2010; Zhang and Thormann, 1996) yielded a higher sensitivity but the instrumental set-up is much more complex and expensive.

4. Conclusion

The proposed methods are quite selective as the drug contains a basic centre, which preferentially interacts with *N*-bromosuccinimide and bromothymol blue. Both the methods show no interference from the common excipients and additives. The statistical parameters and recovery data reveal good accuracy and precision of the proposed methods. Therefore, it is concluded that the proposed methods are simple, sensitive and rapid for the determination of amiodarone hydrochloride in pure form and commercial tablets.

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