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Sensitive Titrimetric And Spectrophotometric Methods For The Assay Of Albendazole In Pharmaceuticals Using Sodium Periodate

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ABSTRACT

Titrimetric and spectrophotometric methods, two each, are described for the assay of albendazole in bulk drug and in tablets using sodium periodate and two dyes, methyl orange and indigo carmine as reagents. In direct titrimetry (method A), albendazole solution is titrated directly with sodium periodate in HCl medium in the presence of potassium bromide to a methyl orange end point. In indirect titrimetry, (method B) an acidic solution of albendazole is treated with a measured excess of periodate in the presence of a large excess of bromide followed by iodometric determination of residual bromine. Spectrophotometric methods involve the addition of a known excess of periodate in acid medium and in the presence of excess of bromide followed by determination of residual bromine by reacting with fixed amount of either methyl orange and measuring the absorbance at 520 nm (method C) or indigo carmine and measuring the absorbance at 610 nm (method D). In all the methods, the amount of periodate reacted corresponds to the amount of albendazole. In both titrimetric methods, the reaction follows a 4:1 (albendazole:$NaIO_4$) stoichiometry and the methods are applicable over 2-18 mg (method A) and 3-20 mg (method B) ranges. In spectrophotometric methods, the absorbance is found to increase linearly with concentration of albendazole which is corroborated by the correlation coefficients of 0.9989 and 0.9986 for method C and method D, respectively, The systems obey Beer's law for 0.5-5.0 μg/ml (method C) and 2.5-25.0 μg/ml (method D). The calculated apparent molar absorptivity values are found to be 2.92×10^4 and 5.11×10^3 l/mol/cm for method C and method D, respectively, and the corresponding Sandell sensitivities are 0.0091 and 0.0052 μg/cm^2. The limits of detection and quantification are reported for both spectrophotometric methods. Intra-day and inter-day precision and accuracy of the described methods were evaluated as per ICH guide lines. The methods were successfully applied to the assay of albendazole in tablets and the results were compared with those of a reference method by applying Student's t-test and F- test. No interference was observed from common tablet adjuvants. The accuracy and reliability of the methods were further ascertained by performing recovery tests by standard addition method.

KEYWORDS Albendazole; Sodium periodate; Titrimetry; Spectrophotometry; Assay.

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INTRODUCTION

Albendazole, chemically known as 5-propyl thio-1H-benzimidazole-2-yl methyl carbamate[1], is used in pharmaceutical practice as an anthelmentic drug with a wide spectrum of activity. Several methods have been reported for the determination of albendazole in dosage forms and in biological fluids. Albendazole has been determined in pure drug and in combined dosage forms with closantel by differential scanning calorimetry (DSC) and high performance liquid chromatography(HPLC)[2]. HPLC has also been used for the assay of the drug in veterinary formulations[3], pharmaceuticals[4], and milk residues[5]. Other methods reported for the assay of albendazole in pharmaceuticals include UV-spectrophotometry[6], first derivative UV-spectrophotometry[7] extractive spectrophotometry using acid dyes[8] and colorimetry using Folin-Ciocalteu reagent [9]. Many titrimetric, spectrophotometric and kinetic methods based on redox and complex formation reactions using bromate-bromide reagent[10,11], chloramine-T[12,13] and N-chlorosuccinimide[14] have also been reported. Very recently[15], titrimetric and spectrophotometric determination of albendazole in non-aqueous medium has also been reported. Although some of the reported methods[10-15] are convenient and sensitive, they are applicable over narrow linear dynamic ranges and employ reagents requiring daily standardization.

Because of simplicity, reasonable accuracy and precision, speed and sensitivity, titrimetry and visible spectrophotometry have withstood the test of time and remained competitive with the newer analytical methods. The present study represents the utilization of sodium periodate as a reagent for the titrimetric and spectrophotometric determination of albendazole. The methods proved to be sensitive, accurate and precise for the determination of albendazole in bulk drug and in pharmaceutical dosage forms.

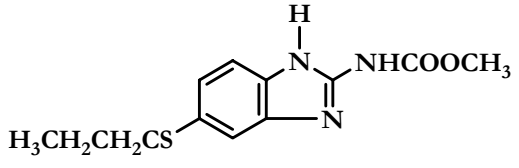

Figure 1: Structure of drug

EXPERMENTAL

Apparatus

A Systronic model 106 digital spectrophotometer provided with 1-cm matched quartz cells was used for absorbance measurements.

Reagents and Solutions

All Chemicals used were of analytical reagent grade and solutions were prepared in distilled water.

Sodium periodate(0.0025 M and 0.005 M)

A stock standard solution (0.01 M) was prepared by dissolving required amount of the chemical (Merck. India. Ltd., Mumbai.) in water. This was appropriately diluted to get 0.0025 M and 0.005 M solutions for use in method A and method B, respectively.

Sodium periodate(15 and 60 μg/ml)

A stock standard solution equivalent to 600 μg/ml $NaIO_4$ was prepared by dissolving accurately weighed 60 mg of the chemical in water and diluting to the mark in a 100 ml calibrated flask. This was appropriately diluted to obtain working concentrations of 15 and 60 μg/ml $NaIO_4$ for use in spectrophotometric method C and method D, respectively,

Sodium thiosulphate

A stock standard solution(0.04 M) was prepared by dissolving about 10 g of the chemical(Sisco Chem Industries, India) in water and diluting to 1 litre, and was used in method B. The solution was diluted to obtain a concentration of 0.02 M for use in method A after standardization with pure dichromate[16]

Potassium bromide(10 and 2%)

A 10% aqueous solution was prepared by dissolving 10 g of the chemical(IDPL, Hyderabad. India) in 100 ml of water and used in titrimetric work, and the same was diluted to 2% for use in spectrophotometric work.

Potassium iodide

A 10% aqueous solution was prepared by dis-

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solving 10 g of the chemical(Qualigens Fine Chem. Mumbai. India) in 100 ml of water.

Methyl orange indicator(0.04%)

Prepared by dissolving 20 mg of the dye (S.D.Fine Chem.Ltd., Mumbai, India) in 50 ml of water.

Methyl orange(50 μg/ml)

A stock standard solution equivalent to 500 μg/ml methyl orange was prepared by dissolving 59 mg of dye(S.D.Fine Chem. Ltd., Mumbai, India; dye content 85%) in water and diluting to the mark in a 100 ml calibrated flask, and filtered using glass wool. This was appropriately diluted to get 50 μg/ml dye solution for spectrophotometric method C.

Indigocarmine(200 μg/ml)

A stock standard solution containing 1000 μg/ml indigocarmine was prepared by dissolving accurately weighed 112 mg dye (S. d. Fine Chem. Ltd., Mumbai, India. dye content 90%) in water and diluted to 100 ml in a calibrated flask, and was diluted to get a working concentration of 200 μg/ml for spectrophotometric method D.

Hydrochloric acid (5 M)

Prepared by diluting 111 ml of concentrated acid (S.D.Fine Chem.Ltd., Mumbai, India, sp. gr. 1.18) to 250 ml with water.

Standard solution of albendazole (ALB)

Pharmaceutical grade albendazole certified to be 99.8% pure was kindly provided by GlaxoSmithkline. Pharm. Ltd., Mumbai. India, as gift and was used as received. A stock standard solution equivalent to 2 mg/ml albendazole was prepared by dissolving 500 mg of pure drug in 50 ml of glacial acetic acid and diluting to 250 ml with water in a calibrated flask and used in titrimetric work. For spectrophotometric study, the stock solution (2000 μg/ml ALB) was diluted stepwise with water to get working concentrations of 25 and 100 μg/ml for method C and method D, respectively.

Procedures

Direct titration (Method A)

A 10 ml aliquot of pure drug solution containing 2-18 mg of ALB was accurately measured and transferred into a 100 ml titration flask, and acidified by adding 2 ml of 5 M HCl. Two ml of 10% KBr solution and 2 drops of methyl orange indicator were added, and titrated with 0.0025 M sodium periodate to a colorless end point. After noting down the volume of periodate consumed, 5 ml of 10% KI solution was added, and the liberated iodine titrated with standard 0.02 M thiosulphate solution using starch indicator. An indicator blank experiment was performed and correction applied. The amount of ALB in the measured aliquot was calculated from:

$$Amount(mg) = \left[\left(V_{NaIO_4} \times M_{NaIO_4}\right) - \left(\frac{V_{thio} \times M_{thio}}{8}\right)\right] M_W \div n$$

Where,

V_{NaIO_4} = volume of sodium periodate consumed, ml

M_{NaIO_4} = concentration of periodate, mol/l

V_{thio} = volume thiosulphate consumed, ml

M_{thio} = concentration of thiosulphate, mol/l

M_w = relative molecular mass of drug

n= number of moles of periodate reacting with each mole of drug.

Indirect titrimetry(Method B)

A 10 ml aliquot of pure drug solution containing 3-20 mg of ALB was accurately measured and transferred into a 100 ml titration flask and acidified by adding 2 ml of 5 M HCl. Two ml of 10% KBr solution followed by 5 ml of 0.005 M sodium periodate were added, the last being measured accurately, The content was mixed well and let stand for 5 min with occasional swirling. Lastly, 5 ml of 10% KI solution was added, and the liberated iodine titrated with 0.04 M thiosulphate using starch as indicator. A reagent blank titration was performed under identical conditions. The amount of ALB in the measured aliquot was computed from:

$$Amount(mg) = \frac{(B - S) M_W R}{n}$$

Where,

B= volume of thiosulphate consumed in the blank titration, ml

S= volume of thiosulphate consumed in the sample titration, ml

M_W= relative molecular mass of drug

R = concentration of periodate solution, mol/l and

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n= number of moles of periodate reacting with each mole of drug.

Spectrophotometry using methyl orange (Method C)

Different aliquots (0.25, 0.5, 0.75—-2.0 ml) of 25 μg/ml ALB solution were accurately measured into a series of 10 ml calibrated flasks by means of a micro burette and the total volume was adjusted to 2 ml by adding water. To each flask were added 2 ml of 5 M HCl and 1 ml each of 2% KBr and 15 μg/ml $NaIO_4$, the last being measured accurately. The content was mixed well and let stand for 10 min with occasional shaking. Lastly, 1 ml of 50 μg/ml methyl orange solution was added to each flask, diluted to the mark, mixed and absorbance of each solution measured at 520 nm against a reagent blank after 5 min.

Spectrophotometry using indigocarmine (Method D)

Varying aliquots(0.25, 0.5, 0.75——2.5ml) of 100 μg/ml ALB solution were accurately measured and transferred into a series of 10 ml calibrated flasks by means of a micro burette and the total volume was brought to 3 ml by adding water. The solution was acidified by adding 2 ml of 5 M HCl, and to each flask was added 1 ml of 2% KBr followed by 1 ml 60 μg/ml $NaIO_4$ the last being measured accurately. The content was mixed well and the flasks were let stand for 5 min with occasional shaking. Finally, 1 ml of 200 μg/ml indigocarmine was added to each flask with the help of a micro burette, the volume was diluted to the mark with water, mixed and absorbance measured at 610 nm against a reagent blank after 5 min.

In either spectrophotometric method, a calibration graph was prepared by plotting the absorbance *vs* concentration or a regression equation derived using the Beer's law data. The concentration of the unknown was read from the calibration graph or computed from the regression equation.

Procedure for tablets

Twenty tablets were accurately weighed and ground into a fine powder. An amount of powder equivalent to 200 mg of ALB was accurately weighed and transferred into a 100 ml calibrated flask, 30 ml of glacial acetic acid added and shaken for about 20 min; the volume was diluted to the mark with water, mixed well and filtered using a Whatman No 42 filter paper. First 10 ml portion of the filtrate was discarded and a convenient aliquot (5 ml) was subjected to analysis by either titrimetric method. The filtrate (2000 μg/ml ALB) was diluted stepwise to get 25 and 100 μg/ml solutions and assayed by taking a suitable aliquot(1or1.5ml).

RESULTS AND DISCUSSION

Preliminary experiments revealed that inconsistent and non-stoichiometric results were obtained when periodate alone was used as the oxidimetric reagent for the titrimetric determination of ALB both in acid and alkaline media (pH 8.5, Politzsch buffer). However, in the presence of potassium bromide, the reaction was found to be feasible in acid medium facilitating even the direct titration of ALB suggesting that *insitu* generated bromine is the actual reacting species in all the methods developed. Except direct titration, the rest of the methods are indirect and are based on the determination of residual bromine (*insitu* generated) after allowing the reaction between ALB and a known amount of bromine to occur. In titrimetry, unreacted bromine is determined iodometrically, and in spectrophotometric methods the same is determined by reaction with a fixed amount of either methyl orange or indigo carmine dye. The spectrophotometric methods make use of bleaching action of bromine on either dye, the decolouration being caused by the oxidative destruction of the dye.

Method development

The reaction was found to be rapid and quantitative in titrimetric analysis when 2 ml of 5 M HCl was used in assay procedures although 1-5 ml of acid did not affect the speed and stoichiometry of the reaction. In indirect titrimetry, the reaction was found to be complete and quantitative in 5 min and standing times up to one hour had no effect on the reaction stoichiometry, Two ml of 10% KBr solution was found adequate in both methods. Direct titration to

methyl orange end point in the presence of KBr was found to yield slightly higher value of 'n' than observed in back titration method (n=0.25). This discrepancy was traced to a small amount of unreacted bromine even after the decolouration of methyl orange. Correct stoichiometry and accurate results were obtained when the amount of residual bromine was determined by iodometric back titration and correction applied.

Employing 0.0025 and 0.005 M periodate in direct titration and back titration methods, 2-18 and 3-20 mg of ALB, respectively, could be determined with a fair degree of accuracy and precision. The relation between the amount of drug and titration end point was examined. The linearity is apparent from the calculated correlation coefficients of 0.9985 and –0.9996 for direct and back titration methods, respectively, suggesting that the reaction between ALB and periodate proceeds stiochiometrically in the ratio 4:1 in the ranges(mg) investigated.

In the proposed spectrophotometric methods, the ability of *insitu* generated bromine to cause oxidation of ALB and irreversibly destroy methyl orange and indigo carmine to colorless products in acid medium has been used. ALB when added in increasing concentrations to a fixed concentration of periodate in the presence of bromide, consumes the *insitu* generated bromine proportionately, and there will be a concomitant fall in the concentration of bromine. When a fixed concentration of either dye is added to decreasing concentration of bromine, a concomitant increase in the concentration of dye results. A proportional increase in the absorbance at the respective λ_{max} is thus observed with increasing concentration of ALB.

Preliminary experiments were performed to fix the upper limits of the dyes that could be determined spectrophotometrically, and these were found to be 5 and 20 μg/ml for methyl orange and indigo carmine, respectively. A $NaIO_4$ concentration of 1.5 μg/ ml in the presence of excess of bromide was found to irreversibly destroy the red color due to 5 μg/ml methyl orange in acid medium whereas 6.0 μg/ml $NaIO_4$ was required to cause similar action on 20 μg/ml indigo carmine in acidic conditions. Hence, different amounts of ALB were reacted with 1 ml of 15μg/ ml $NaIO_4$ in method C and 1 ml of 60 μg/ml $NaIO_4$ in method D followed by determination of residual oxidant as described under respective procedures.

For the oxidation of ALB by bromine and the bleaching of dye by the latter, hydrochloric acid was found to be identical. Two ml of 5 M acid in a total volume of about 6-7 ml was adequate for the oxidation step, which was complete in 5 min, and the same acid concentration was maintained for the bleaching step. Neither the acid concentration nor the reaction time was critical, and 1-5 ml of 5 M HCl and reaction times up to 30 min produced the same absorbance values for a given ALB concentration. A 5 min contact time was found necessary for bleaching of dye color by the residual bromine. The absorbance of either dye color was stable for several hours in the presence of the reaction product.

Analytical parameters of the spectrophotometric methods

A linear relation is found between absorbance and concentration in the ranges given in TABLE 1. The graphs showed negligible intercept and are described by the equation:

$$Y = a + b X$$

(where Y = absorbance; a = intercept; b = slope and X = concentration in μg ml^{-1}) obtained by the method

TABLE 1: Analytical parameters of the spectrophotometric methods

Parameter	Method A	Method B
λ_{max}, nm	520	610
Beer's law limits, μg/ ml	0.5-5.0	2.5-25.0
Molar absorptivity, l /mol/ cm	2.92×10^4	5.11×10^3
Sandell sensitivity, μg /cm^2	0.0091	0.0052
Limit of detection, μg/ml	0.10	0.55
Limit of quantification, μg/ ml	0.30	1.66
Regression equation, Y*		
Intercept (a)	-0.0068	-0.0121
Slope (b)	0.1144	0.0208
Sa	9.10×10^{-3}	9.12×10^{-3}
Sb	2.24×10^{-3}	4.5×10^{-4}
Correlation coefficient (r)	0.9989	0.9986

Y= a + bX where Y is the absorbance and X concentration in μg/ ml
Sa=Standard deviation of intercept
Sb= Standard deviation of slope

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of least squares. Correlation coefficients, intercepts and slopes for the calibration data are also presented in TABLE 1. Sensitivity parameters such as molar absorptivity and Sandell sensitivity values, and the limits of detection and quantification, are also presented in TABLE 1.

Method validation

Evaluation of accuracy and precision

Intra-day and accuracy were assessed from the results of seven replicate analyses on pure drug solution. The mean values and relative standard deviation (RSD) values for replicate analyses at three different amount/concentration levels were calculated. To determine the inter-day precision, analysis was performed over a period of five days preparing all solutions afresh each day. The accuracy of the methods was determined by calculating the percentage deviation observed in the analysis of pure drug solution and expressed as the relative error (RE). TABLE 2 summarizes the intra-day precision and accuracy data for the determination ABZ by the proposed methods which were within 3%. The inter-day precision was less than 3.5%.

Application to tablets analysis

The Indian pharmaceutical industry has currently made available 47 brands of tablets containing ABZ for human use. Three representative brands of tablets each containing 400 mg of ABZ per tablet were assayed by the proposed methods and the results are summarized in TABLE 3. The results obtained were compared with those obtained by an established UV-spectrophotometric method[6] which consisted of the

TABLE 2: Intra-day accuracy and precision of the methods

Method*	ALB taken	ALB found**	Range	Relative error,%	SD	SDM	RSD %	ROE %
A	5.0	4.87	0.66	2.6	0.09	0.034	1.86	±4.85
	10.0	9.98	0.27	0.2	0.101	0.038	1.01	±1.00
	15.0	14.99	0.27	0.07	0.107	0.040	0.71	±0.71
B	5.0	4.93	0.26	1.4	0.083	0.031	1.68	±2.67
	10.0	9.93	0.26	0.7	0.144	0.054	1.45	±1.44
	15.0	15.24	0.27	1.6	0.142	0.053	0.93	±0.93
C	1.25	1.24	0.018	0.8	0.009	0.003	0.70	±0.70
	2.50	2.49	0.06	0.4	0.031	0.012	1.26	±1.25
	3.75	3.74	0.04	0.27	0.018	0.007	0.48	±0.49
D	5.0	5.05	0.24	0.92	0.101	0.038	2.00	±2.00
	10.0	9.90	0.09	1.00	0.041	0.015	0.41	±0.41
	15.0	14.85	0.15	1.00	0.053	0.020	0.36	±0.35

****Mean value of seven determinations**

In methods A and B, ALB taken/found, range, SD and SDM are in mg, and in methods C and D, they are in μg/ ml.

SD. Standard deviation; SDM. Standard deviation of mean;

RSD. Relative standard deviation and ROE. Range of error at 95% confidence level for six degrees of freedom.

TABLE 3: Results of assay of tablets by the proposed methods

Brand name of tablet*	Nominal amount, mg	Reference method	% found**± SD			
			Method A	Method B	Method C	Method D
Albendol[a]	400	101.5±0.64	99.74±1.1 t=3.19 F=2.95	100.3±0.74 t=2.75 F=1.34	99.96±1.5 t=2.27 F=5.49	102.6±0.85 t=2.33 F=1.76
Alminth[b]	400	98.46±1.2	99.78±0.66 t=2.24 F=3.31	97.58±0.85 t=1.36 F=1.99	100.1±1.6 t=1.85 F=1.78	99.66±1.7 t=1.30 F=2.01
Tobend[c]	400	100.4±0.88	101.3±0.58 t=1.95 F=2.3	99.48±0.96 t=1.58 F=1.19	101.3±1.4 t=1.25 F=2.53	102.1±1.3 t=2.46 F=2.18

***Marked by: a. Micro Labs; b. Torrent Pharma; c. Cipla India. Ltd.**

****Mean value of five determinations**

Tabulated value of t at 95% confidence level is 2.77

Tabulated value of F at 95% confidence level is 6.39

measurement of absorbance of the tablet extract in 0.01% acetic acid at 292 nm. A close agreement between the results obtained by the proposed methods and the reference method in terms of accuracy and precision was obtained as evident from the calculated Student's t value and F-value (TABLE 3). The results also agreed well with the label claim.

Accuracy and validity of the methods were further ascertained by performing recovery experiments *via* standard addition technique. To a fixed and known amount of ABZ in tablet powder (pre analysed), pure drug was added at three levels and the total was found by the proposed methods. Each test was repeated three times. The recovery of pure ABZ added to tablet powder ranged from 95.5 to 105.1% (TABLE 4) indicating that commonly encountered tablet excipients and additives such as talk, starch, lactose, sodium alginate, magnesium stearate calcium gluconate and calcium dihydrogenorthophosphate did not interfere in the assay procedure.

TABLE 4: Results of recovery study by standard addition method

Method	Formulation studied	ALB in formulation	Pure ALB added	Total found	Pure ALB recovered %
A	Alminth 400 mg	2.99	2.0	5.09	105.1
		2.99	4.0	6.97	99.56
		2.99	6.0	9.04	100.85
B		4.88	5.0	9.74	97.10
		4.88	10.0	14.73	98.5
		4.88	15.0	20.15	101.8
C		20.02	10.0	29. 57	95.5
		20.02	20.0	40.52	102.5
		20.02	30.0	49.33	97.7
D		49.8.3	50.0	99.63	99.60
		49.83	100.0	148.3	98.5
		49.83	200.0	250.23	101.2

****Mean value of Three determinations**
In methods A and B, ALB in formulation/added, total found, are in mg, and in methods C and D, they are in μg.

In conclusion, four new methods for the assay of albendazole in pharmaceuticals using $NaIO_4$ as the oxidimetric reagent have been developed and appropriately validated. The methods are simple, rapid and cost effective. The titrimetric methods are the most sensitive ever developed for albendazole and are applicable over a semimicro scale, (2-20 mg). Both spectrophotometric methods are based on well-characterised redox reactions and are more sensitive over the existing methods for albendazole in pharmaceuticals. The sensitivity is better than many HPLC methods in terms of linear range of applicability and this has been achieved using as simple a technique as visible spectrophotometry. The stability of the coloured species and sensitivity of the reactions used are not critically dependent on any experimental variable unlike many reported methods. All the methods are based on the use of $NaIO_4$ which is exceptionally stable solution. These advantages coupled with a fairly degree of accuracy and precision qualify the methods for use in quality control laboratories.

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