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Kinetic and Titrimetric Determination of Albendazole Using Bromate and Methyl Orange

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Two methods, kinetic and titrimetric, based on bromination reaction with bromine, are described for the assay of albendazole in bulk drug and in tablets. The kinetic method depends on the linear relationship between the concentration of the drug (μg/ml) and time (s) for bromination, as indicated by bleaching of methyl orange acid colour. The titrimetric method is based on the direct titration of the drug with standard bromate solution in the presence of excess of bromide and in hydrochloric acid medium using methyl orange as indicator. Kinetic method is applicable in the concentration range of 5 to 25 μg/ml, and using titrimetry, 3 to 20 mg of drug can be determined with a fair degree of accuracy and precision. Tablet excipients donot interfere in either method. Recoveries of drug added to commercial formulations were good. As indicated by t- and F- values, the methods are as accurate and precise as the reference method.

Albendazole, chemically known as 5-propyl thio-IH-benzimidazol-2-yl methyl carbamate[1], is used in pharmaceutical practice as an anthelmentic drug with a wide spectrum of activity. Albendazole has been assayed in pure drug and in combination 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 are UV-spectrophotometry[6], first-derivative UV-spectrophotometry[7], extractive spectrophotometry using acid dyes[8] and colorimetry using Folin-Ciocalteu reagent[9]. In search of new methods for the assay of albendazole, kinetic and titrimetric investigations of the reaction between albendazole and bromate-bromide solution in the presence of methyl orange have been examined.

The most widely used brominating agent is bromate-bromide solution first proposed by Francis[10]. The bromine generated on adding acid to bromate-bromide solution was used to brominate albendazole molecule. The kinetic method described here is based on the linear relationship between bromination time and concentration of drug. The titrimetric method is based on the titration of drug to a colourless end point using methyl orange as indicator.

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MATERIALS AND METHODS

All reagents used were of analytical reagent grade. Double distilled water was used throughout the experiment. Methyl orange solution for kinetic studies was prepared by dissolving 47 mg of methyl orange (S.D. Fine Chem., Mumbai, 85% dye content) in 1 litre of 1 M sulphuric acid. A mixture of 0.01M potassium bromate-0.02 M potassium bromide was prepared by dissolving 1.67 g of $KBrO_3$ (Sarabhai Chem., Vadodara) and 2.38 g of KBr (S. D. Fine Chem. Mumbai) in water and diluting to 1 litre in a volumetric flask for kinetic method. $KBrO_3$ (0.02 M) was prepared by dissolving 0.835 g of reagent in water and diluting to mark in 250 ml volumetric flask. The solution was further diluted to get 0.002 M potassium bromate for titrimetric work. Potassium bromide (10%) and methyl orange indicator solution were prepared in the usual way. Hydrochloric acid (5 M) was prepared by diluting 350 ml of concentrated acid (S. D. Fine Chem., Mumbai) to 1 litre with water.

Pure albendazole was kindly provided by M/s Cipla

India Ltd., Mumbai, and was used as received. Five hundred milligrams of albendazole was dissolved in minimum amount of acetic acid and diluted to mark in 250 ml volumetric flask to provide a concentration of 2 mg/ml. This was diluted to obtain a concentration of 100 µg/ml for kinetic work.

Twenty to 40 tablets depending on the content per tablet were weighed and finely powdered. An accurately weighed portion equivalent to 200 mg of albendazole was transferred into 100 ml volumetric flask, 20 ml glacial acetic acid and 40 ml of water were added and shaken thoroughly for about 20 min. Then, the volume was made up to the mark, mixed well and filtered using a quantitative filter paper. First 10 ml of filtrate was rejected and a suitable aliquot of the filtrate was treated as described under the procedure for titrimetric determination. The filtrate was diluted to get 100 µg/ml solution and a convenient volume was used for kinetic analysis as described below.

For titrimetric work, a 10 ml aliquot of pure drug solution containing 3 to 20 mg of albendazole was accurately measured into a *100 ml titration* flask followed by the addition of 5.0 ml of hydrochloric acid and 5.0 ml of 10% potassium bromide. The contents were mixed well and titrated with bromate (0.002 M) solution using methyl orange as indicator till the discharge of indicator colour. A blank determination was run, and the volume was subtracted from the volume required for sample titration.

In kinetic method, 5, 10, 15, 20 and 25 ml aliquots of drug solution (100 µg/ml) were transferred into separate 50 ml volumetric flasks containing 25 ml of methyl orange solution (40 µg/ml) and diluted to volume with water. In to separate test tubes of similar dimensions, 5.0 ml of the above prepared solution and 5.0 ml of 0.01 M $KBrO_3$–0.02 M KBr solution were accurately measured. Both the tubes were immersed in an ice bath until they reached 4 to 5°. The stop clock (accurate to 0.2 s) was started and the two solutions were thoroughly mixed noting the time of addition (initial time T_i). The time required for methyl orange colour to discharge was noted (final time, T_f). The actual time (T_e) was computed, where, $T_e=T_f-T_i$. A blank experiment was carried out simultaneously by mixing bromate–bromide solution with methyl orange solution, omitting addition of drug. Bleaching time (T_b) for blank experiment was recorded. The corrected (T_c) time was computed using $T_c=T_e-T_b$. A calibration curve was prepared by plotting T_c as a function of concentration of drug or the regression equation was calculated using the bleaching time and concentration data. The concentration of the unknown was read from the calibration curve or computed using the regression equation.

RESULTS AND DISCUSSION

Bromination was found to be much faster than the rate of bromine production following addition of acid to bromate–bromide solution at room temperature (32±2°). However, by employing small concentration of drug and decreasing the reaction temperature to 4 to 5°, a small steady state concentration of bromine, which acts as a chemical clock, is setup; a rate that approximately the monobromination rate. The sharp increase in bromine production after monobromination is sufficient to discharge the acid colour of methyl orange, and the time of bleaching is directly proportional to the concentration of the drug. Extrapolation of the linear relationship intercepts the time axis at a point almost equal to the blank reading. The experimental reading can therefore be corrected. The calibration curve of time (T_c in s) Vs concentration (C) in the range of 5 to 25 µg/ml calculated from the final dilution after methyl orange addition can be described by the following regression equation derived by the method of least squares[11]. $T_c=0.4290-$

TABLE 1: ACCURACY AND PRECISION

Titrimetric method					Kinetic method				
Amount taken, mg	Amount Found*, mg	Range	% error	RSD, % (n= 7)	Amount taken, µg	Amount Found*, µg	Range	% error	RSD , % (n= 7)
1.0	1.01	0.05	1.0	1.76	50	50.23	0.32	0.46	1.92
1.5	1.51	0.60	0.60	1.53	100	98.90	0.24	1.10	0.69
2.0	2.03	0.29	1.50	4.53	150	148.79	0.85	0.81	1.59

*Average of seven determinations

TABLE 2: COMPARISON OF RESULTS OF ALBENDAZOLE DETERMINATION BY THE PROPOSED METHODS AND REFERENCE METHOD

Formulation*	Label claim mg/ tablet	FoundΨ (%recovery ± SD)		
		Titrimetry (T)	Kinetic (K)	Reference method
Alminth[a]	200	99.2±0.31	98.4±0.81	99.7±0.56
Albental[b]	400	99.8±1.15	102.6±2.12	101±0.92
Zentel[c]	400	98.7±0.31	98.9±0.51	99.3±0.44
Zoleban[d]	500	99.2±1.33	101.±1.21	100.8±0.86
Nopar[e]	400	99.8±1.04	98.2±0.74	99.4±0.78

*Marketed by: [a]Torrent, [b]Micro labs, [c]Smith Kline Beecham, [d]Combat Drugs, [e]Malladi Drugs, ΨAverage of five measurements

0.2372 C. The regression coefficient for the above relationship was calculated to be 0.9951.

The titrimetric determination of albendazole is based on the bromination by bromine produced *in situ* by the reaction of bromate with bromide in acid medium. The titrations were carried out in hydrochloric acid medium, 5 ml of 5M acid being optimum in a total volume of about 25 to 30 ml.

The relationship between the titration end points obtained by this method and the drug amounts was examined. The linearity between the amount of the drug and titrimetric endpoint is apparent from the correlation coefficient, r obtained by determining the best fit line via linear least squares treatment. The correlation coefficient of 0.9992 shows that the reaction between bromine and albendazole proceeds stiochiometrically in a molar ratio 1:1 as shown in Fig. 1.

The accuracy and precision of the methods were assessed by analysing the pure drug at three levels each repeated seven times. The percent error and relative standard deviation (%) values presented in Table 1. reveal the acceptable accuracy and precision of the proposed methods. The proposed methods were applied to the analysis of certain commercial formulations containing albendazole

TABLE 3: RESULTS OF RECOVERY STUDIES BY STANDARD – ADDITION METHOD

Formulation	Titrimetric method				Kinetic method			
	Amount of drug in formulation (mg)	Amount pure drug added (mg)	Total found* (mg)	% recovery of pure drug (±SD)	Amount of drug in formula-ton (µg)	Amount pure drug added (µg)	Total found* (µg)	% recovery of pure drug (±SD)
Alminth (200 mg)	2.97	5.00	7.77	96.00±1.26	49.20	50.00	99.89	101.38±2.05
	2.97	10.00	12.74	97.70±1.34	49.20	100.0	150.2	101.0±1.28
	2.97	15.00	17.71	98.27±1.76	49.20	150.0	198.2	99.54±1.72
Zentel (400 mg)	2.96	5.00	8.13	103.4±1.62	49.45	50.00	100.1	101.26±0.86
	2.96	10.00	13.12	101.6±2.42	49.45	100.0	150.2	100.7±2.21
	2.96	15.00	17.70	98.3±1.54	49.45	150.0	199.8	100.2±1.75
Nopar (400 mg)	2.99	5.00	8.13	102.8±0.66	49.01	50.00	99.59	101.2±0.54
	2.99	10.00	12.76	97.70±1.76	49.01	100.0	148.8	99.80±1.98
	2.99	15.00	18.16	101.1±0.26	49.01	150.0	195.2	97.47±1.34

*Average of three measurements

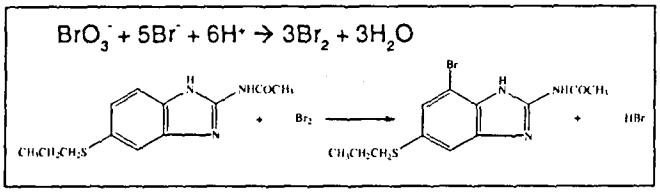

Fig. 1: Reaction Scheme

and the results are compiled in Table 2. Statistical analysis by the variance ratio test and Student's t-test showed that there was no significant difference between the performance of the proposed methods and the reference method[12] at the 95% confidence level since the calculated t-values were less than 2.77 (tabulated value) and F-values were less than 6.39 (tabulated value). To study the reliability of the proposed methods a standard addition method was followed. A fixed amount of albendazole from tablets was taken and pure albendazole at three different levels was added and the total amount of the drug was determined by the proposed methods. Each determination was repeated three times. The amount of pure drug added in each instance was then found by difference. The results of this study are summarized in Table 3, which indicate that lactose, starch, magnesium stearate, sodium alginate and talc which are commonly incorporated as excipients did not interfere.

Both methods are fast, accurate and reproducible and do not require expensive instrumentation. Therefore, they are well suited for routine analysis and quality control of albendazole in tablets.

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