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Spectrophotometric determination of butylated hydroxyanisole in pure form, cosmetics, food and pharmaceutical products

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Abstract
New and rapid spectrophotometric methods have been developed for the determination of butylated hydroxyanisole (BHA) in pure form, cosmetics, food, and pharmaceutical products. These methods are based on the oxidation of the BHA in acidic medium then a known concentration of dye was added and the unreacted oxidant was estimated using UV-Vis spectrophotometer. Beer's law was obeyed in the concentration range of 2.0-40, 5.0-110, 4.0-60 µg/mL for method (I), (II), and (III), respectively. The proposed procedures were successfully applied to assay BHA in pure form, cosmetics, food and pharmaceutical products. The obtained results showed good agreement with those given by the standard methods.

Keywords: Butylated hydroxyanisole; Spectrophotometry; Redox reaction; Dosage forms.
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1. Introduction

Antioxidants are pharmacological active molecules which prolongs the shelf-life of food, cosmetics, and pharmaceutical industries by protecting them against deterioration caused by oxidation such as fat rancidity and loss of nutrient value [1-3]. The protection mechanism of antioxidant is capable of delay or inhibit the oxidation of a substance which caused by free radicals that is oxidized easily even in low concentrations [4,5]. Antioxidants are defined by the U. S. Food and Drug Administration (FDA) as food preservatives that specifically retard deterioration, rancidity, or discoloration due to lipid oxidation [6]. Butylated hydroxyanisole is synthetic antioxidant which added directly to many types of products such as food, pharmaceuticals, cosmetics and petroleum products [7-10]. BHA (Fig. 1) is a phenolic antioxidant which consisting of a mixture of two isomeric organic compounds, 2-tert-butyl-4-hydroxyanisole and 3-tert-butyl-4-hydroxyanisole [11-14]. Several studies have shown that some of synthetic antioxidants have harmful effects on human health [15]. Therefore, some governments have taken heed to these limitations of some synthetic antioxidants and are now banning and placing a restriction on their use. According to the existing food additive regulations published by the U S food and drug administration, the use of BHA is permitted individually or combined up to a maximum limit of 0.02% or 200 parts per million [16,17].[7]

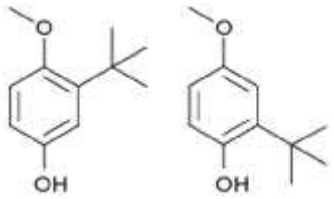

Fig.1. Chemical structure of butylated hydroxyanisole (BHA)

BHA is harmful when swallowed, inhaled, or absorbed through skin. It is irritating to the skin, eyes, mucous membranes, and upper respiratory tract. Prolonged or repeated exposure may cause allergic reactions in certain sensitive individuals. The target organs for toxicity are liver, lungs, and forestomach [18]. BHA has been found to be tumour-producing when fed to animals such as rat. In human studies it has been linked with urticaria, angioedema and asthma [19].

A variety of analytical methods for determining BHA including spectrophotometry [20-23], fluorescence [14], Electrochemical [25-27], voltammetry [28-30], and chromatography [31-35].

The aim of this present study was to develop simple and reproducible spectrophotometric methods for the determination of BHA by oxidation of the BHA in acidic medium.

2. Experimental

Apparatus

All absorption spectra were made using JASCO V-670 UV/Vis spectrophotometer (Japan) with a scanning speed of 200 nm/min and a band width of 2.0 nm, equipped with 10 mm matched quartz cells.

Reagents

All chemicals and reagents used were of analytical grade and all solutions were prepared in doubly distilled water. A stock standard solution of BHA (100 µg mL^{-1}) was prepared by dissolving an exact weight (10 mg) of BHA (loba- india) in 5 mL N, N-Dimethylformamide in 100 mL measuring flask and diluted to the mark with bidistilled water. A solution of 2.0 M of sulfuric acid was prepared by transfer dropwise addition of 10.9 mL of concentrated solution of the acid (loba-india Sp. gr. 1.84, 98.0 %) to 50 mL bidistilled water in 100 mL measuring flask and diluted to the mark. The solution was standardized with 1.0 M Na_2CO_3 according to published method.[36] 1.0 M of hydrochloric acid was prepared by transfer 8.27 mL of concentrated solution of the acid 37.2 % to 100 mL measuring flask and diluted to the mark with distilled water the solution was standardized with 1.0 M Na_2CO_3 according to published method [36]. $1x10^{-3}$ M of $KMnO_4$ is prepared by dissolving 0.0158 g of pure sample of $KMnO_4$ in 50 mL bidistilled water in 100 mL measuring flask and diluted to the mark. The permanganate solution was standardized against sodium oxalate by standard procedure [37]. A solution of 100 µg mL^{-1} (5.62×10^{-4} M) of NBS ($C_4H_4O_2NBr$) was prepared by dissolving 10 mg of NBS in 10 mL of warm distilled water in 100 mL measuring flask, then diluted to the mark with distilled water. Cerium ammonium sulphate (IV) solution of concentration 0.75 mg/mL was prepared by dissolving 75 mg Ce $(NH_4)_4(SO_4)_4.H_2O$ in 100 mL of 0.25 M of sulfuric acid. A solution of 1.0% KBr was prepared by dissolving 1 g of KBr in 10 mL of warm distilled water in 100 mL measuring flask, and then diluted to the mark with distilled water. A solution of 2×10^{-3} M methyl orange [4-dimethylaminoazobenzene-40-sulfonic acid sodium salt], was prepared by dissolving 0.0654 g of dye in distilled water and diluting to 100 mL in a measuring flask with distilled water. A solution of $1x10^{-3}$ M methylene blue dye is prepared by dissolving 0.0391 g of pure sample of methylene blue in 50 mL bidistilled water in 100 mL measuring flask and diluted to the mark. Aqueous solution of amaranth dye was prepared by dissolving 0.12088 g in 20 mL of warm distilled water in 100 mL measuring flask, then diluted to the mark with distilled water.

General procedure

Method (I)

Aliquots (0.1–2.0 mL) of the standard BHA solution (100 µg mL^{-1}) were transferred to 10 mL measuring flask and excess volume of oxidant $KMnO_4$ (0.6 mL $1x10^{-3}$ M) was added and the optimum volume of H_2SO_4 (2.0 M) was transferred. After oxidation process had completed, a known volume of methylene blue dye was added, and the unreacted oxidant $KMnO_4$ was estimated by measuring the decrease in absorbance of methylene blue at the suitable wavelength (667nm), against corresponding reagent blank similarly prepared.

Method (II)

In 10 mL calibrated flasks accurate volumes of BHA solution (100 µg mL^{-1}) were transferred, excess volume of oxidant cerium ammonium sulphate (0.75 mg/mL) was added and the optimum volume of H_2SO_4 (2.0 M) was transferred. After oxidation process had completed, a known volume of amaranth dye was transferred and the unreacted oxidant cerium ammonium sulphate was determined by measuring the decrease in absorbance of Amaranth dye at the suitable wavelength (520 nm), against corresponding reagent blank similarly prepared.

Method (III)

Accurate volumes of BHA solution (100 µg mL^{-1}) was transferred in 10 mL calibrated flasks, add excess volume of oxidant N-bromosucccinimide ($5.62x10^{-4}$ M) was transferred and the optimum volume of HCl (1.0 M) was added. After oxidation process had completed, a known volume of methyl orange dye was added and the unreacted oxidant N-bromosucccinimide was determined by measuring the decrease in absorbance of methyl orange dye at the suitable wavelength (481 nm), against corresponding reagent blank similarly prepared.

Procedure for assay of pharmaceutical formulations

Aliquot containing 10 g from oil, cream, tablet or melted fat was dissolved in 25 mL tert-butanol then this solution was put in centrifuge for 1 minute then the solution was placed in water bath 40-50 °C for 15 minutes, the upper layer was poured into 50 mL calibrated flask, the extraction process repeated with 20 mLtert-butanol then 1.0 mL was taken in 10 mL calibrated flask then diluted to the mark.

3. Results and discussion

The proposed methods are based on the oxidation of BHA by adding an excess of an oxidant in an acidic medium and then left for fixed time to enhance the oxidation process of the BHA.

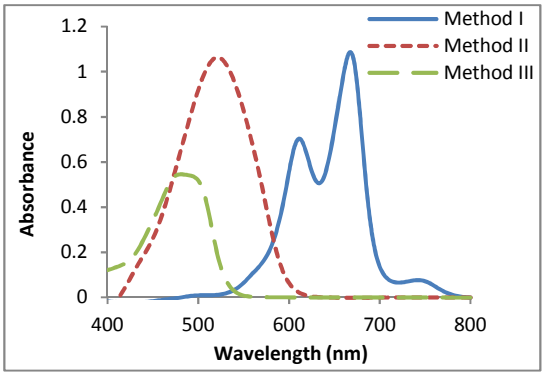

Fig. 2. Absorption spectra for the reaction product of 30 µg of BHA with 1 mL of oxidants and 0.7 mL of dyes.

After the oxidation of the BHA was completed, the unreacted oxidant was reacted with a fixed quantity of dye and the resulting change in absorbance was measured at 667 nm for using potassium permanganate method (Methods I), whereas for cerium ammonium sulphate method at 522 nm (Methods Π) and for N-bromosucccinimide method 481 nm (Methods Ш) (Fig. 2).

Optimization

The influences of each of the following variables on the oxidation reaction of materials were examined to achieve the maximum color intensity.

1- Effect of acid concentration

Methods (I) and (Π)

The sulphuric acid was found most appropriate for methods (I) and (Π) .In order to determine the optimum acid volume facilitating the oxidation process, different volumes of H_2SO_4 (2.0) M was studied in the range 0.1-2.0 mL in a total volume 10 mL under the reaction conditions: 0.6 ml of $KMnO_4$ ($1X10^{-3}$ M) and added 0.4 of methylene blue dye were added for methods (I) and 1.5 ml of CAS (0.75 mg mL^{-1}) and 0.3 of amaranth dye were transferred for methods (Π). The results presented in Fig. 3 indicated that, 0.4 mL of 2.0 M H_2SO_4 was the optimum volume for method (I) and 0.5 mL for method (Π) thoughout the study.

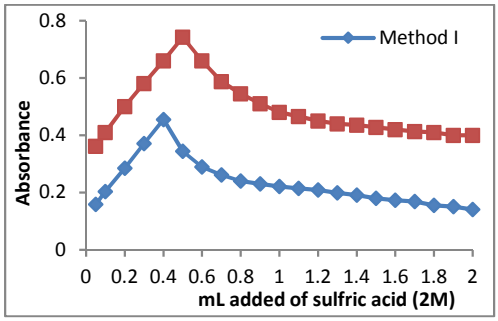

Fig. 3. Effect of sulfuric acid concentration on the oxidation of 30 µg of BHA with 0.6 mL of KMnO4 ($1X10^{-3}$ M) and 0.4 of methylene blue dye for method (I) and 1.5 mL of CAS (0.75 mg mL^{-1}) and 0.3 of amaranth dye for method (Π).

Method III:

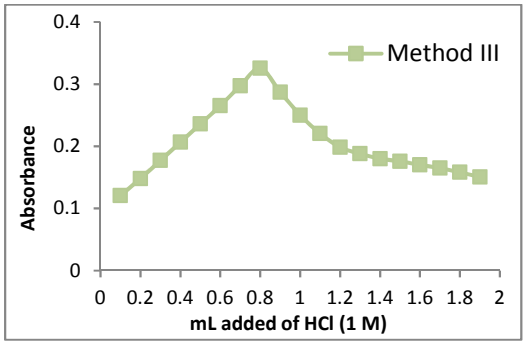

Fig. 4. Effect of hydrochloric acid concentration on the oxidation of 30 µg of BHA with 0.8 mL of NBS ($5.62X10^{-4}$ M) and 0.4 mL of methyl orange dye.

The hydrochloric acid was suitable for this method. The effect of HCl (1.0 M) was studied in the range 0.1-2.0 mL in a total volume 10 mL. 0.8 mL of NBS ($5.62X10^{-4}$ M) and 0.4 of methyl orange dye were added. The results presented in Fig. 4 indicated that, 0.8 mL of 1.0 M HCl was applied throughout the study.

2- Effect of time and temperature

The reaction time was studied by standing the BHA solution after mixing with oxidant for different intervals time. The results indicated that 5.0 min was required to complete the reaction for all methods. The results are presented in Fig. 5. The effect of time after addition the dye was studied by measuring the absorbance at various time intervals (1.0-5.0 min). The absorbance indicated that shaken for one minute is sufficient to give reliable results. The effect of temperature was studied by heating the sample solution and the blank at different temperature (25-50 °C). The optimum temperature was found to be the ambient (25 ±1 °C).

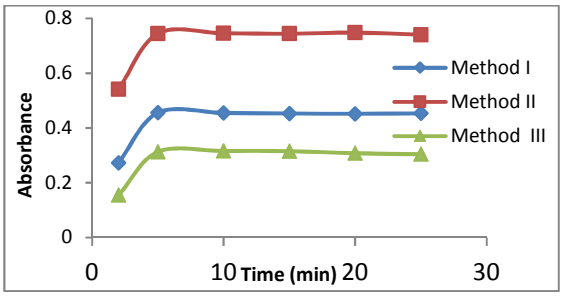

Fig. 5. Effect of shaking time on the oxidation of 30 µg of BHA with 0.6 mL of $KMnO_4$ ($1X10^{-3}$ M), 0.4 mL of 2.0 M H_2SO_4 and 0.4 of methylene blue dye for method (I) and 1.5 mL of CAS (0.75 mg mL^{-1}), 0.5 mL of 2.0 M H_2SO_4 and 0.3 of amaranth dye for method (Π) and 0.8 mL of NBS ($5.62X10^{-4}$ M), 0.8 mL of 1.0 M HCl and 0.4 mL of methyl orange dye.

3- Effect of sequence of addition

Effect of sequence of addition on the oxidation process of the BHA was studied by measuring the absorbance of solutions prepared by different sequence of addition against a blank solution prepared in the same manner. The results showed that (BHA- Acid- Oxidant and then the dye) gave the best results. Other sequences gave lower absorbance values under the same experimental conditions.

4- Effect of KBr concentration

Using catalyst on the oxidation process of BHA is useful to reduce the time required to complete the oxidation process. To study the effect of KBr concentration on oxidation process, the concentration of the BHA, acid, oxidant and dye are kept constant and the volumes of 1.0 % KBr is regularly varied (0.1 - 2.0 mL). The absorption spectra were recorded against blank solution prepared in the same manner without BHA. The resulting spectra showed that for method (I), (II) there is no effect of the presence of KBr because the redox reactions between bromide ions and

sulfuric acid. The bromide ions reduce the sulphuric acid to sulphur dioxide gas where the bromide ions are oxidised to bromine, whereas for method (III) 0.6 mL of KBr is optimum volume required accelerating the oxidation process as shown in (Fig. 6).

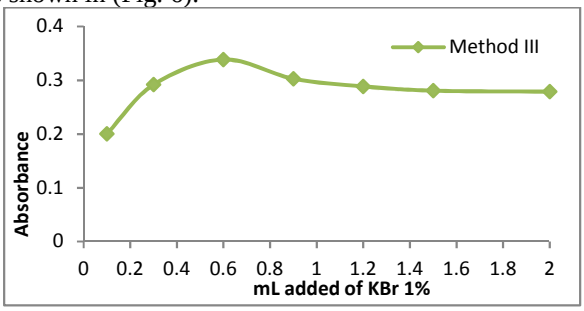

Fig. 6. Effect of KBr concentration on the oxidation of 30 µg of BHA with 0.8 mL of NBS (5.62X10-4 M), 0.8 mL of 1.0 M HCl and 0.4 of methyl orange dye.

5- Effect of dye volume

The effect of dye volume was studied by adding different concentrations of MB, AM and MO in method (I), (Π) and (Ш), respectively, to the proposed concentration of BHA. The optimum volume used for production of maximum and reproducible color intensity was found to be 0.4, 0.7 and 0.8 mL for method (I), (Π) and (Ш), respectively, as shown in (Fig. 7).

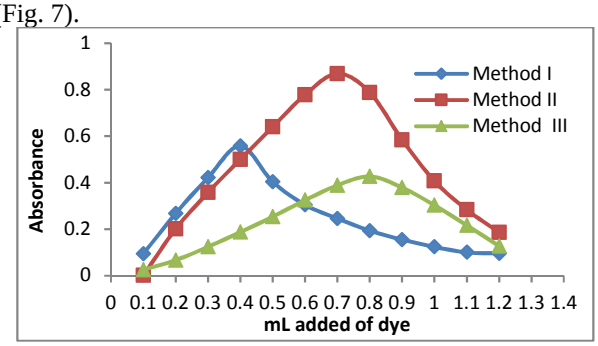

Fig. 7. Effect of Effect of dye volume on the oxidation of 30 µg of BHA with 0.6 mL of $KMnO_4$ ($1X10^{-3}$ M), 0.4 mL of 2.0 M H_2SO_4 for method (I) and 1.5 mL of CAS (0.75 mg mL^{-1}), 0.5 mL of 2.0 M H_2SO_4 for method (Π) and 0.8 mL of NBS ($5.62X10^{-4}$ M), 0.8 mL of 1.0 M HCl.

Analytical validity

The linear regression equations, standard deviation, slopes and intercepts, correlation coefficients, relative standard deviation of response factors, and linearity ranges were given in (Table 1) for each proposed spectrophotometric method.

Table 1 Statistical analysis of calibration graphs and analytical data in the determination of BHA by oxidation methods.

Parameters	Method (I)	Method (Π)	Method (Ш)
λ max (nm)	667	522	481
Beer´ s law limits (µg mL^{-1})	2.0 - 40	5.0 - 110	4.0 - 60
Ringbom limits (µg mL^{-1})	7.0 - 35	8.0 - 105	10 - 55
Molar absorptivity(1 mol^{-1} cm^{-1})	4.371×10^3	1.616×10^3	1.434×10^3
Sandell sensitivity (µg cm^{-2})	0.041	0.11	0.12
Detection limits (µg mL^{-1})	0.069	0.042	0.011
Quantitation limits (µg mL^{-1})	0.230	0.139	0.037
Slope (b)	0.0098	0.0101	0.0082
Intercept (a)	- 0.0298	- 0.0058	0.0112
Correlation coefficient	0.9994	0.9991	0.9995

A = a + bC (where C is the concentration in µg mL^{-1}).

Sensitivity, accuracy, and precision

The mean molar absorptivity (ε) and Sandell sensitivity (S) as calculated from Beer's law are presented in Table 1. In order to determine the accuracy and precision of the method, solutions containing seven different concentrations of BHA were prepared and analyzed. The measured standard deviation (SD), relative standard deviation (RSD.), the standard analytical errors (SAE) and confidence limit are listed in (Table 2).

Table 2 Evaluation of accuracy and precision

Method	Added	Recovery	RSD	RE	Confidence limit
I	20	100.5	0.71	0.5	20.1 ±0.62
	25	99.6	0.62	-0.4	24.9 ±0.54
	30	99	0.55	-1.0	29.7 ±0.48
	35	100.6	0.50	0.57	35.2 ±0.44
	40	99.25	0.41	0.75	40.24 ±0.36
П	20	99.5	0.91	-0.50	19.9 ±0.8
	25	100.8	0.85	0.00	25.2 ±0.75
	30	100.3	0.74	0.30	30.09 ±0.65
	35	99.4	0.60	-0.57	34.79 ±0.53
	40	99.7	0.94	-0.25	39.88 ±0.82
Ш	20	100.7	0.65	0.75	20.14 ±0.57
	25	99.2	0.75	-0.8	24.80 ±0.66
	35	100.25	0.6	0.25	35.09 ±0.51
	40	99	0.46	-1.0	39.6 ±0.4

4. Conclusions

New, simple and highly sensitivity methods have been described for determination of BHA in pure form, cosmetics, food, and pharmaceutical products. The methods are based on oxidation of BHA in acidic medium then known volume of dye was added and the unreacted oxidant was determined by measuring the decrease in absorbance of dye at the suitable wavelength. An excess amount of oxidant was added first over the sample solution. After completing the BHA oxidation, a suitable volume of dye was added and the absorbance of the final solution was then measured. The experimental parameters of the method have been optimized, a critical importance presenting the order of reagents addition and the time of BHA oxidation. The methods are accurate, reproducible, adequately sensitive. The wide applicability of the new procedures for routine quality control is well established by the assay of BHA in pure form, cosmetics, food and pharmaceutical products.

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