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USE OF ECO-FRIENDLY BROMINATING AGENT FOR THE SPECTROPHOTOMETRIC DETERMINATION OF CARBAMAZEPINE IN PHARMACEUTICAL FORMULATIONS

SAMEER ABDULAZIZ MOHAMMED ABDULRAHMAN, KANAKAPURA BASAVAIAH*, HOSAKERE DODDAREVANNA REVANASIDDAPPA AND KANAKAPURA BASAVAIAH VINAY
Department of Chemistry, University of Mysore, Manasagangotri, Mysore 570006, Karnataka, India

We describe two sensitive spectrophotometric methods for the determination of carbamazepine (CBZ) either in pure form or in pharmaceutical formulations. These methods are based on the bromination of CBZ by the bromine generated in situ from the bromate-bromide reaction. The methods involved the addition of a known excess of bromate-bromide reagent in acid medium to CBZ. After the reaction was complete, the unreacted bromine was determined by reacting with a fixed amount of either fluorescein sodium (FS) and measuring the absorbance at 510 nm (method A) or with rosaniline hydrochloride (RAH) and measuring the absorbance at 570 nm (method B). Beer's law was obeyed in the concentration ranges of 0.45–3.00 μg/mL of CBZ with molar absorptivity of 5.37×10^4 L/mol/cm for method A and 0.50–3.50 μg/mL of CBZ with molar absorptivity of 5.19×10^4 L/mol/cm for method B. The proposed methods were successfully applied to the determination of CBZ in tablets and syrup with good accuracy and precision and without detectable interference from common excipients. The validity and reliability of the proposed methods were further assessed by the recovery studies via a standard addition method. These methods have the advantages of avoiding the use of liquid bromine and offering cost-effective analyses.

Keywords: *Carbamazepine assay, Spectrophotometry, Bromate-bromide, Fluorescein sodium, Rosaniline hydrochloride*

INTRODUCTION

Carbamazepine (CBZ), chemically known as 5H-dibenz[b,f]-azepine-5-carboxamide (Merck Index 2006), is a type of tricyclic drug which is frequently used in the treatment of trigeminal neuralgia and as an anticonvulsant. The British Pharmacopeia (Department of Health and Social Security 1973) describes a UV-spectrophotometric method for its assay in tablets. The literature on the methods for the determination of CBZ in biological materials using different techniques is vast (120 articles published). In contrast, a limited number of techniques have been reported for the determination of CBZ in pharmaceutical dosage forms which includes liquid chromatography (LC) (Walker 1988; Panchagnula *et al*. 1998; Yuan, Jun and McCall 2003; Demirkaya and Kadioglu 2005; Tatar Ulu 2006; Demirkaya and Kadioglu 2008; Džodić *et al*. 2009), gas chromatography (GC) (Liu, Wu and Zou 1991; Kadioglu and Demirkaya 2007), flow injection (FI)-spectrophotometry

*Corresponding author: Kanakapura Basavaiah, e-mail: basavaiahk@yahoo.co.in

(Çomoğlu *et al.* 2006), FI-spectrofluorimetry (Huang, He and Chen 2002), chemiluminescence (CL) spectrometry (Lee, Li and Suh 2003), FI-CL spectrometry (Xiong *et al.* 2009), electrolysis-fluorescence spectrometry (Pan and Yao 1998), polarography (Pachecka and Giovanoli 1982), UV-spectrophotometry (Tatar Ulu 2006; Demirkaya and Kadioglu 2008) and visible spectrophotometry (Rao and Murty 1982; Agrawal, Giridhar and Menon 1989).

Many previously reported methods for the determination of CBZ require expensive instruments or materials. In addition, chromatographic methods (Walker 1988; Liu, Wu and Zou 1991; Panchagnula *et al*. 1998; Yuan, Jun and McCall 2003; Tatar Ulu 2006; Kadioglu and Demirkaya 2007; Džodić *et al*. 2009) need a suitable compound as an internal standard, which makes the procedure more complex. The major advantages of visible spectrophotometric methods are its simplicity and cost effectiveness, and also being fairly sensitive and easily accessible. To the best of our knowledge, there are only two reports on the use of visible spectrophotometry for the determination of CBZ in pharmaceuticals. The first report is by Rao and Murty (1982) and is based on the oxidation of CBZ with sodium metaperiodate in acidic medium after heating for 1 hour, followed by extraction of the chromogen into n-butanol before measuring the absorbance at 410 nm. The second method by Agrawal, Giridhar and Menon (1989) is based on the reaction of amide group in CBZ with hydroxylammonium chloride-NaOH under hot conditions, followed by reaction with ferric chloride in HCl medium and measuring the absorbance at 510 nm. The visible spectrophotometric methods currently available (Rao and Murty 1982; Agrawal, Giridhar and Menon 1989) involve extraction or heating step.

In this paper, we report the development and optimisation of two sensitive procedures for the determination of CBZ in pure form as well as in its dosage forms. The developed methods utilise bromate-bromide mixture in acid medium as an eco-friendly brominating agent and two dyes, viz., fluorescein sodium (FS) and rosaniline hydrochloride (RAH) as auxiliary agents.

METHODS

Apparatus

All absorbance spectral measurements were made using a Systronics Model 106 digital spectrophotometer (Systronics, Ahmedabad, Gujerat, India) provided with 1 cm matched quartz cells.

Materials and Reagents

Pharmaceutical grade CBZ was received from Jubilant Organosys Ltd., Mysore, India, as a gift and used as received. All pharmaceutical preparations were obtained from commercial sources in the local market. All reagents and chemicals used were of analytical reagent grade and distilled water was used throughout the study.

A stock standard solution of bromate-bromide mixture equivalent to 1000 µg/mL $KBrO_3$ and 10-fold molar excess of KBr was prepared by dissolving accurately weighed 100 mg of potassium bromate (S. D. Fine-Chem Ltd., Mumbai) and 712 mg of potassium bromide (Merck, Mumbai) in water and diluting to volume in a 100 mL calibrated flask. It was diluted with water to obtain the working concentrations of 30.0 and 40.0 µg/mL in $KBrO_3$ for method A and method B, respectively.

Solutions of 2 M hydrochloric acid (HCl) (Merck, Mumbai, sp. gr. 1.18), 10 M acetic acid (CH_3OOH) (Merck, Mumbai, sp. gr. 1.05), 8 M sulphuric acid (H_2SO_4) (Merck, Mumbai, sp. gr. 1.84), 10 M sodium hydroxide (NaOH) (Merck, Mumbai), 0.015% FS (BDH Chemicals Ltd., England) solution for method A, were prepared in water. Solution of 75 µg/mL RAH (S. D. Fine-Chem Ltd., Mumbai) was prepared in 2 M H_2SO_4 and tert-butanol (Merck, Mumbai) was used without any purification.

A stock standard solution equivalent to 500 µg/mL CBZ was prepared by dissolving accurately weighed 50 mg of pure drug in 20 mL methanol and diluted to the mark in a 100 mL calibrated flask with water. It was diluted appropriately with water to get the working concentrations of 15 and 20 µg/mL CBZ for use in method A and method B, respectively.

Assay Procedures

Method A (using FS)

Different aliquots (0.0–2.0 mL) of a standard CBZ (15 µg/mL) solution were accurately transferred into a series of 10 mL calibrated flasks and the total volume was adjusted to 2.0 mL by adding adequate quantity of water. To each flask was then added 1.0 mL of 2 M HCl and 1.0 mL of bromate-bromide mixture (30 $\mu g/mL^{-1}$ in $KBrO_3$) and the content was mixed well and kept aside for 10 min. Then, 2 mL of 10 M acetic acid was added followed by 1.0 mL of 0.015% FS solution. After 5 min, 2.0 mL of 10 M NaOH was added and the flasks were made up to 10 mL with water. The flasks were allowed to cool before measuring the absorbance at 510 nm against a water blank.

Method B (using RAH)

Aliquots (0.00–1.75 mL) of a standard CBZ (20 µg/mL) solution were accurately transferred into a series of 10 mL calibrated flasks and the total volume was adjusted to 2.0 mL by adding adequate quantity of water. To each flask 2.0 mL of 8 M H_2SO_4 was added followed by 1.0 mL of bromate-bromide mixture (40 µg/mL in $KBrO_3$) and the content was mixed well and kept aside for 15 min. 1 mL of 75 µg/mL RAH solution was added and after 5 min, 2.5 mL of tert-butanol was added followed by 1.0 mL of 8 M H_2SO_4. The flasks were made up to 10 mL with water and the absorbance of each solution was measured at 570 nm against a water blank.

Assay procedure for tablets

Ten tablets containing CBZ were accurately weighed and ground into a fine powder. A portion of the powder equivalent to 40 mg of CBZ was accurately weighed into a 100 mL calibrated flask; 16 mL of methanol and 50 mL of water were then added. The content was shaken for 15–20 min; the volume was diluted to the mark with water, mixed well and filtered using a Whatman No. 42 filter paper. The first 10 mL portion of the filtrate was discarded and the filtrate was appropriately diluted with water to get 15 and 20 µg/mL of CBZ for the assay by method A and method B, respectively.

Assay procedure for syrup

2 mL of syrup (Tegrital 100 mg/5 mL) equivalent to 40 mg of CBZ was transferred into a 100 mL calibrated flask, 16 mL of methanol and 50 mL of water were then added. The content was shaken for 15–20 min; the volume was diluted to the mark with water and mixed well. The resulting solution was clear and it was appropriately diluted with water to get 15 and 20 µg/mL of CBZ for the assay by method A and method B, respectively.

Statistical Analysis

The statistical Student's t-test was used to compare the results obtained by the proposed methods and the reference UV spectrophotometric method (Department of Health and Social Security 1973). The tabulated t-value for 4 degrees of freedom at the 95% confidence level is 2.78 and the calculated t-value was recorded using the following equations (Lung *et al*. 2003; Christian 2004):

$$t = \frac{\left|\bar{x} - \bar{y}\right|}{S_P}\sqrt{\frac{n_x n_y}{n_x + n_y}}, \quad S_P = \sqrt{\frac{(n_x - 1)S_x^2 + (n_y - 1)S_y^2}{(n_x - 1) + (n_y - 1)}}$$

where $\bar{x}$ and $\bar{y}$ are the means of the two methods, n_x and n_y are the number of individual results obtained by the two methods, S_x and S_y are the standard deviation of the two methods; and S_P is the pooled standard deviation.

Also, F-test was applied to compare the precision of the proposed methods with the precision of the reference method. The tabulated F-value for both 4 degrees of freedom at the 95% confidence level is 6.39 whereas the calculated F-value was found using the following equation (Lung *et al*. 2003; Christian 2004):

$$F = \frac{S_x^2}{S_y^2}, \text{ where } S_x^2 > S_y^2.$$

RESULTS

Effect of Experimental Variables

Effect of reagent concentration

Preliminary experiments were performed to study the effect of the two dyes viz. fluorescein and rosaniline to achieve higher sensitivity for the proposed methods. The results showed that 1.0 mL of 0.015% of FS gave a maximum absorbance and 7.5 µg/mL of RAH was the highest concentration that could be determined spectrophotometrically. Bromate concentrations of 3.0 and 4.0 µg/mL in the presence of a large excess of bromide was found optimum to produce maximum coloured products with fluorescein and

rosaniline dyes, respectively. Hence, different concentrations of CBZ were reacted with 1.0 mL of 30 µg/mL bromate in method A (FS) and 1.0 mL of 40 µg/mL bromate in method B (RAH) in acid medium and in the presence of a large excess of bromide followed by the determination of residual bromine as described under methods A and B.

Effect of reaction media

In method A, HCI was found to be ideal to liberate the bromine from bromate-bromide mixture and 1.0 mL of 2 M HCl was found to be optimum to produce maximum absorbance. Also, acetic acid was found to be the best medium for the bromination of the fluorescein by the residual bromine to form eosin and 2.0 mL of 10 M acetic acid was found to be optimum. Finally, the addition of NaOH solution was necessary to increase the pH (~5.5–5.6) to form a stable and maximum colour intensity product and it was found that 2.0 mL of 10 M NaOH is required.

In method B, a high acid concentration was necessary to retain the colour of the bromo derivative product and for maximum suppression of the colour of the rosaniline solution to avoid any interference from a small excess of rosaniline. Hence, 3.0 mL of 8 M H_2SO_4 was used in the assay. Also, the addition of tert-butanol was necessary since the bromorosaniline is insoluble in aqueous acid medium in which it was formed (Hunter and Goldspink 1954).

Reaction time and colour stability

Under the conditions described above, the reaction between CBZ and in situ bromine took 10 and 15 min in method A and method B, respectively, whereas the bromination of the dyes by the residual bromine was found to be completed in 5 min for both methods. The absorbance of the measured coloured product was constant for more than 2 hrs and 45 min for method A and method B, respectively, even in the presence of the reaction products.

Method Validation

Analytical parameters

Under optimum experimental conditions for CBZ determination, the standard calibration curves were constructed by plotting the absorbance *versus* concentration (Fig. 1). Beer's law was obeyed over the concentration ranges (Table 1), and the linearity of the calibration graphs was demonstrated by the high values of the correlation coefficient (r) and the small values of the y-intercepts of the regression equations. The regression parameters were calculated from the calibration graphs data along with molar absorptivity. Sandell sensitivity are also presented in Table 1.

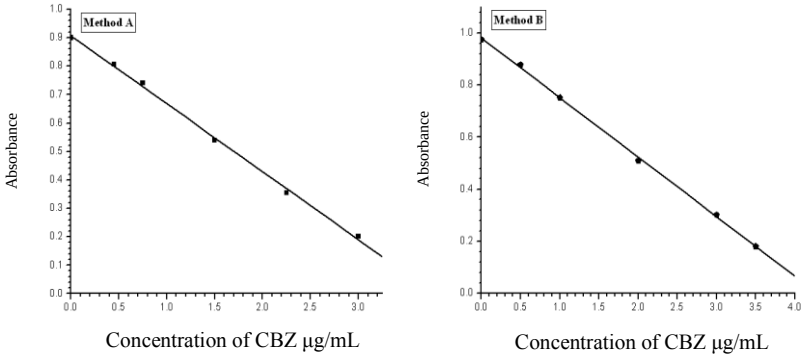

Fig. 1: Calibration curves for method A (FS) and method B (RAH).

Table 1: Analytical and regression parameters.

Parameter	Method A	Method B
λ_{max}, nm	510	570
Beer's law limits (µg/mL)	0.45–3.00	0.50–3.50
Molar absorptivity (L/mol/cm)	5.37×10^4	5.19×10^4
Sandell sensitivity* (µg/cm²)	0.0044	0.0045
Limit of detection (µg/mL)	0.14	0.26
Limit of quantification (µg/mL)	0.42	0.80
Regression equation, Y**=	0.9070–0.2390X	0.9809–0.2287X
Correlation coefficient (r)	0.9990	0.9996
Standard deviation of intercept (S_a)	0.0089	0.0069
Standard deviation of slope (S_b)	0.0053	0.0033

Notes: *Limit of determination as the weight in µg per mL of solution, which corresponds to an absorbance of A = 0.001 measured in a cuvette of cross-sectional area 1 cm² and l = 1 cm. **$Y = a + bX$, where Y is the absorbance, *a* is the intercept, *b* is the slope and *X* is the concentration in µg/mL.

Sensitivity

The limit of detection (LOD) for the proposed methods was calculated using the following equation (ICH 2005):

$$LOD = \frac{3.3 \times \sigma}{S}$$

where σ is the standard deviation of replicate determination values under the same conditions as for the sample analysis in the absence of the analyte and S is the sensitivity, namely the slope of the calibration graph. In accordance with the formula, the detection limits were found to be 0.14 and 0.26 µg/mL for method A and method B, respectively.

The limit of quantitation (LOQ), is defined as (ICH 2005):

$$LOQ = \frac{10 \times \sigma}{S}$$

According to this equation, the quantitation limits were found to be 0.42 and 0.80 µg/mL for method A and method B, respectively.

Accuracy and precision

In order to determine the precision of the proposed methods, solutions containing three different concentrations of CBZ were prepared and analysed in seven replicates and the analytical results were summarised in Table 2. The low values of the relative standard deviation percentage (%RSD) and relative error percentage (%RE) indicate the high precision and the good accuracy of the proposed methods. RSD (%) and RE (%) values were obtained within the same day to evaluate repeatability (intra-day precision) and over five days to evaluate intermediate precision (inter-day precision).

Table 2: Evaluation of intra-day and inter-day precision and accuracy.

Method*	CBZ taken (µg/mL)	Intra-day (n = 7)			Inter-day (n = 5)		
		CBZ found[a] (µg/mL)	%RSD[b]	%RE[c]	CBZ found[a] (µg/mL)	%RSD[b]	%RE[c]
A	0.75	0.77	2.62	2.67	0.78	3.45	4.00
	1.50	1.53	3.04	2.00	1.55	3.09	3.33
	2.25	2.29	1.75	1.78	2.31	2.21	2.67
B	1.00	0.97	2.58	3.00	0.97	2.91	3.00
	2.00	1.98	2.09	1.00	1.96	2.46	2.00
	3.00	2.93	1.83	2.33	2.90	1.87	3.33

Notes: [a]Mean value of n determinations, [b]relative standard deviation (%), [c]bias (%): [(found – taken) / taken] ×100

Selectivity

In order to evaluate the selectivity of the proposed methods for the analysis of pharmaceutical formulations, the effect of the presence of common excipients, such as talc, starch, lactose, glucose, sodium alginate, calcium gluconate and magnesium stearate was tested for possible interference in the assay by placebo blank and synthetic mixture analyses and no significant interference was observed from these excipients.

Application to assay of pharmaceutical formulations

The proposed methods were successfully applied to the determination of CBZ in formulations (tablet and syrup) (Table 3). The results obtained were statistically compared with those of the reference method (Department of Health and Social Security 1973) by

applying the Student's t-test for accuracy and F-test for precision. The reference method consisted of measurement of the absorbance of the alcoholic extract of the tablets at 285 nm. From Table 3, it is clear that the calculated t-value and F-value at 95% confidence level did not exceed the tabulated values of 2.78 and 6.39 respectively, for 4 degrees of freedom. The results indicated that there is no difference between the proposed methods and the reference method with respect to accuracy and precision.

Table 3: Comparison of assay results by proposed and reference methods.

Tablet brand name	Nominal amount	Found (% of nominal amount ± SD)*		
		Reference method	Proposed methods	
			Method A	Method B
Zeptol tablets[a]	100 mg	100.3±0.64	99.02±1.36 **t =** 1.90 **F** = 4.52	98.22±1.43 **t =** 2.97 **F** = 4.99
Tegrital Syrup[b]	100 mg/5 mL	97.56±0.72	97.32±1.09 **t =** 0.41 **F** = 2.29	96.58±1.51 **t =** 1.31 **F** = 4.40

Notes: *Mean value of five determinations±SD.
**Marketed by: [a]Sun Pharmasikkim, Ranipool, India; [b]Piramal Healthcare Limited, Mahad, India.
Tabulated t-value at the 95% confidence level is 2.78; tabulated F-value at the 95% confidence level is 6.39.

Recovery study

Accuracy and validity of the proposed methods was further ascertained performing recovery experiments via the standard addition procedure. Tablet powder or syrup (pre-analysed) spiked with known amounts of pure CBZ at three different concentration levels (50%, 100% and 150% of the quantity present in the tablet powder or syrup) was analysed by the proposed methods to determine the recoveries of pure drug added (Table 4).

DISCUSSION

The solution of bromate-bromide mixture in acid medium behaves as an equivalent solution of bromine and it has been used for the assay of several compounds of pharmaceutical interest (Basavaiah 2006; Basavaiah and Anil Kumar 2007; Basavaiah *et al.* 2007; El-Didamony 2010; El-Didamony and Erfan 2010). The present work deals with two spectrophotometric methods for the determination of CBZ using bromine generated in situ as eco-friendly brominating agent. Bromine generated in situ by the action of the acid on bromate-bromide mixture replaced the use of highly toxic and hazardous liquid bromine. The developed methods are based on the bromination reaction of CBZ with a measured excess of bromate-bromide mixture in acid media, and after the bromination of CBZ was complete, the residual bromine generated in situ was then used to brominate the fluorescein and rosaniline yielding coloured bromo derivatives products absorbed maximally at 510 and 570 nm, respectively (Fig. 2). The amount of in situ bromine reacted corresponded to the amount of CBZ which formed the basis of the assay.

Many experimental variables were carefully optimised to achieve higher sensitivity for the proposed methods. The developed methods are superior to all previously reported spectrophotometric methods of Çomoğlu *et al.* (2006) [2.55–15.3 µg/mL with LOD of 0.20 µg/mL]; Tatar Ulu (2006) [4.0–10.0 µg/mL with LOD of 1.25 µg/mL]; Demirkaya and Kadioglu (2008) [1.25–25 µg/mL with LOD of 0.25 µg/mL]; Rao and Murty (1982) [10–100 µg/mL]; Agrawal, Giridhar and Menon (1989) [4–80 µg/mL]. The sensitivity of the proposed methods (lower limit of the linear range was as low as 0.45 and 0.5 µg/mL with LOD values of 0.14 and 0.26 µg/mL for methods A and B, respectively) is higher than that of all reported spectrophotometric methods described above (the lowest limit reported for the linear range was 1.25 µg/mL) for the determination of CBZ in pharmaceuticals.

Table 4: Results of recovery study by standard-addition method.

Formulation studied	CBZ in formulation (µg/mL)	Pure CBZ added (µg/mL)	Total found (µg/mL)	Pure CBZ recovered* (percent±SD)
Zeptol (100 mg)	**Method A**			
	0.89	0.45	1.33	97.78 ± 2.06
	0.89	0.90	1.81	102.2 ± 1.99
	0.89	1.35	2.26	101.5 ± 2.05
	Method B			
	0.98	0.50	1.49	102.0 ± 1.74
	0.98	1.00	2.01	103.0 ± 2.88
	0.98	1.50	2.50	101.3 ± 1.73
Tegrital (100 mg/ 5 mL)	**Method A**			
	1.17	0.60	1.79	103.3 ± 2.28
	1.17	1.20	2.39	101.7 ± 1.08
	1.17	1.80	3.01	102.2 ± 2.67
	Method B			
	1.16	0.60	1.77	101.7 ± 2.86
	1.16	1.20	2.35	99.17 ± 1.95
	1.16	1.80	2.91	97.22 ± 2.82

Note: *Mean value of three determinations±SD.

Reaction Mechanism

The reaction between CBZ and bromine generated in situ by the action of the acid on bromate-bromide mixture uses electrophilic substitution as well as addition reactions. The presence of the nitrogen atom attached to the benzene rings will direct the bromination to *ortho* and *para* positions in both the rings but the bromination occurs at the *para* positions only due to the steric effect of the amide group, which leads to a decrease in the amount of the ortho-product. The addition of the bromine will occur at the olefinic double bond on the central heterocyclic ring of CBZ (Fig. 3).

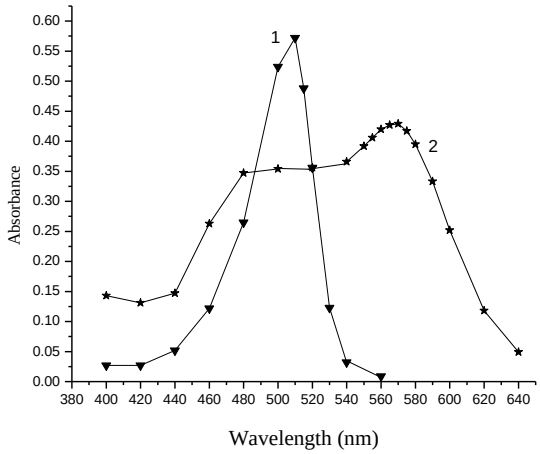

Fig. 2: Absorption spectra of brominated dyes; 1. FS (method A), 2. RAH (method B).

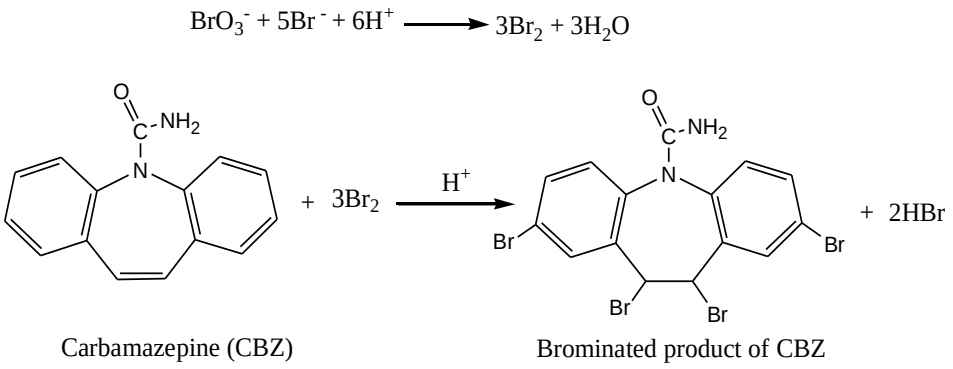

Fig. 3: Bromination of CBZ.

The reaction of unreacted bromine with fluorescein has been reported to form a pink coloured product (Orndorff and Hemmer 1927; Pohl 1956) due to the bromination of the fluorescein and formation of tetrabromo derivative or eosin. Similarly, the unreacted bromine reacts with rosaniline to yield a purple coloured product of tetrabromorosaniline (Hunter and Goldspink 1954; Hunter 1955; Goodwin 1971) (Fig. 4).

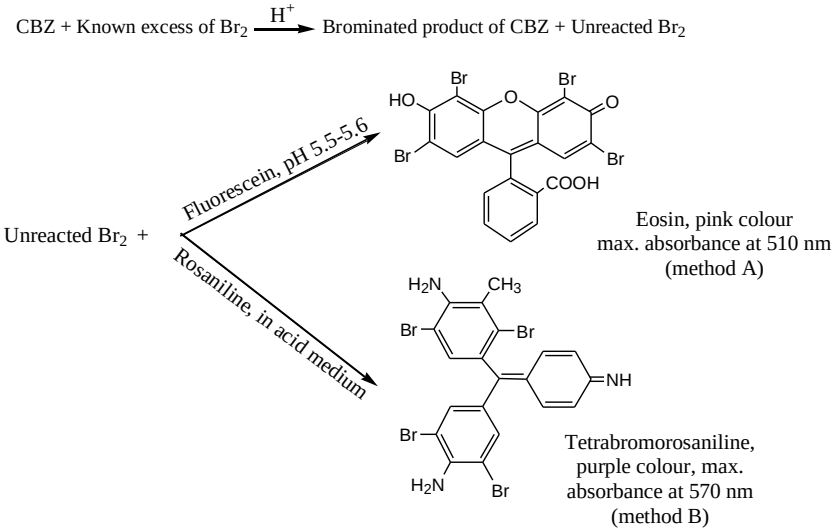

Fig. 4: Tentative reaction scheme for the proposed methods.

CONCLUSION

The findings demonstrate that it is possible to use a bromate-bromide solution as an eco-friendly brominating agent for the determination of CBZ in authentic samples. The proposed methods are free from experimental variables such as heating or extraction step. They rely on the use of simple, cheap and readily available chemicals and techniques but provide sensitivity comparable to that achieved by sophisticated and expensive technique like HPLC. Thus, they can be used as alternatives for rapid and routine determination of bulk sample and formulations in quality control laboratories.

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