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Spectrophotometric Determination of Carbamazepine in Pharmaceutical Formulations Based on its Reaction with a Brominating Agent

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Abstract

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Keywords

Bromate-bromide, Carbamazepine, Cresol red, Methylene blue, Spectrophotometry

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RESEARCH ARTICLE

Spectrophotometric Determination of Carbamazepine in Pharmaceutical Formulations Based on its Reaction with a Brominating Agent

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ABSTRACT

Two accurate spectrophotometric methods described for the estimation of carbamazepine (CBZ) in both pharmaceutical and pure form. These methodologies are attached to the bromination of CBZ by bromine formed in instantly from the bromate-bromide reaction. The general procedure includes the additional of a known amount of bromate-bromide reagent in an acidic mediocre to CBZ. After the reaction is integrated, the unreacted bromine was reacted with a steady amount of methylene blue, and the absorbance was measured at 665 nm (method A) or, cresol red could be used for the reaction and the absorbance moderated at 517 nm (method B). Beer's law was submitted from 0.45 to 15.00 µg/mL CBZ with a molar absorptivity of 4.93×10^3 L/mol.cm for method A and from 0.50 to 12.00 µg/mL CBZ with a molar absorptivity of 1.37×10^4 L/mol.cm for method B. The proposed methods were effective for the determination of CBZ in tablets with great precision and accuracy.

Keywords: Bromate-bromide; Carbamazepine; Cresol red; Methylene blue; Spectrophotometry

INTRODUCTION

Carbamazepine (CBZ), also familiar as 5H-dibenz[b,f]-azepine-5-carboxamide (Index et al., 2006), is a tricyclic, mood stabilizing, an anticonvulsant drug which is often used in the therapy of bipolar disorder, and neuropathic soreness epilepsy. The drug is mentioned in the British Pharmacopoeia (2013) which expresses a high-performance liquid chromatography (HPLC) method for its dissection in tablet form (Abdulrahman et al., 2010).

The literature regarding the processes for the specification of CBZ in biological materials using different techniques is wide: LC (Džodić et al., 2009; Walker, 1988), flow injection (FI) spectrophotometry (Çomoğlu et al., 2006), FI chemiluminescence (CL) (Xiong et al., 2009), Gas chromatography (GC) (Liu et al., 1991; Kadioglu and Demirkaya, 2007), HPLC (Panchagnula et al., 1998; Yuan et al., 2003; Demirkaya and Kadioglu, 2005; Demirkaya and Kadioglu, 2008; Ulu, 2006), polarography (Zhang et al., 1993), FI-spectrofluorimetry (Huang et al., 2002), CL (Lee et al., 2003; Abed and Al-Abachi, 2015), and visible spectrophotometry (Rao and Murty, 1982; Agrawal et al., 1989).

Numerous instruments and materials have been used to detect pharmaceutical, including CL, FI, and chromatographic techniques (Walker, 1988; Liu et al., 1991; Panchagnula et al., 1998; Yuan et al., 2003; Demirkaya and Kadioglu, 2008; Džodić et al., 2009). However, many of these techniques involve complex procedures and require pretreatment. The procedural simplicity of visible spectrophotometry and its cost-effectiveness, selectivity, sensitivity, acceptable accuracy, good precision, and widespread availability in quality control laboratories make it a useful technique.

To the best of our knowledge, only one titrimetric method has been reported (Basavaiah and Abdulrahman, 2014), and many reports for the specification of CBZ in pharmaceuticals have involved the use of visible spectrophotometry. Rao and Murty, 1982, described a method established on the oxidation reaction between sodium metaperiodate and CBZ in the acidic moderate after heating for 1 h. Before measuring the absorbance at 410 nm, the chromogen must be extracted into n-butanol. Agrawal et al., 1989, demonstrated a method established on the reaction of hydroxyl ammonium chloride–NaOH with the amide group in CBZ under hot provisions, follow-up by reaction with ferric chloride in an HCl-containing moderate and measurement of the absorbance at 510 nm. Frag et al., 2012, reported the charge transfer and ion pair complexation reactions between CBZ and mosapride

citrate. Another method described (Fadhel et al., 2017) sensitive spectrophotometric determination of CBZ, established on the oxidation of 2,4-dinitrophenylhydrazine by potassium periodate and coupling with CBZ in a base medium to form a stable yellowish-brown water-soluble dye with maximum absorption at 485 nm. It is clear that researchers use visible spectrophotometry because of its accuracy, precision, and simplicity.

Herein, we report the optimization of two sensitive procedures for the determination of CBZ in dosage and pure forms. The developed methods utilize a bromate-bromide mixture in acidic moderate as well as methylene blue (MB) and cresol red (CR) as auxiliary agents.

Instruments

All the spectral absorbance estimations were performed utilizing a Labomed, Inc., U.S.A. Advanced spectrophotometer furnished with a 1 cm coordinated cell.

REAGENTS AND MATERIALS

Pure CBZ standard powder was obtained from the State Company for Drug Industries and Medical Appliances, Samara-Iraq (SDI). All other chemical reagents were provided by "Awamedica" in Erbil-Iraq. Every single pharmaceutical tablet was conveyed from trading sources in the provincial market. All synthetic substances and reagents utilized were of analytical reagent grade and distilled water was utilized along the study.

CBZ Stock Solution (1000 µg/mL)

A stock standard arrangement of CBZ at a concentration of 1000 µg/mL was set up by melting 100 mg of naive material in 20 mL of ethanol at that point diluting it to 100 mL with D.W in a 100 mL volumetric flask.

Hydrochloric Acid Solution (1.0 mol/L)

The 1.0 mol/L HCl arrangement was set up by diluting 41.45 mL of concentrated HCl in a 500 mL volumetric flask with distilled water. The arrangement was standardized utilizing a Na_2CO_3 solution.

Potassium Bromate Solution (4.7×10^{-3} mol/L)

A stock standard arrangement of potassium bromate $KBrO_3$; 4.7×10^{-3} mol/L was set up by dissolve 0.196 g of $KBrO_3$ in a 250 mL volumetric flask with water. Other solutions were prepared daily from the standard solution by serial dilution in a 100 mL calibrated flask.

Potassium Bromide Solution (4.7×10^{-2} mol/L)

A stock standard arrangement of potassium bromide KBr; 4.7×10^{-2} mol/L was set up by dissolve 1.398 g of KBr in a 250 mL volumetric flask with water. Other solutions were prepared daily from the standard solution by serial dilution in a 100 mL volumetric flask.

MB Solution (3.1×10^{-4} mol/L)

In advance, 1×10^{-2} g of MB powder was dissolved in 50 mL of water, at that point diluted in a 100 mL volumetric flask with water to set up (3.1×10^{-4} mol/L) the final MB solution.

CR Solution (2.4×10^{-3} mol/L)

In advance, 1×10^{-2} g of CR powder was dissolved in 20 mL of water, at that point diluted in a 100 mL calibrated flask with water to set up (2.4×10^{-4} mol/L) the final CR solution.

Assay Procedure for Tablets

A sum of 10 tablets, including CBZ, were ground into a fine powder and precisely weighed (486 mg) then dissolved in a 200 mL calibrated flask. Subsequently, 100 mL of ethanol was included and the flask was mechanically shaken for 15 min. The blend was then weakened to mark with water, blended and strained thoroughly Whatman filter paper no 42. Then, 5 mL of the solution was diluted to 50 mL with ethanol:water (1:1) diluent.

Spectrophotometry using MB (Method A)

Into a progression of 25 mL volumetric flasks, 1.0 mL of 1 mol/L HCl was added follow-up by 2.0 ml of bromate-bromide (1.0 mL of potassium bromate [4.7×10^{-4} mol/L] and 1.0 mL of potassium bromide 4.7×10^{-3} mol/L]). The flask was let to stand for 1 min (Time 1) with snatchy shaking. Subsequently, 3 ml of 100 µg/mL CBZ (12 µg/mL) was suffixed to a flask and allowed to equilibrate for 2 min (Time 2). After that, (4 mL of 3.1×10^{-3} mol/L) MB solution was added to the mixture and diluted to the flask volume with water and stirring well (Time 3). Afterward, the absorbance of the arrangement was measured at 665 nm.

Spectrophotometry using CR (Method B)

Into a series of 25 mL calibrated flasks, 1.0 mL of 1 mol/L HCl was added follow-up by 2.0 mL of bromate-bromide (1.0 mL of potassium bromate [4.7×10^{-4} mol/L] and 1.0 mL of potassium bromide [4.7×10^{-3} mol/L]). The flask was let to stand for 1 min (Time 1) with snatchy shaking. Then, 3 mL of 100 µg/mL CBZ (8.0 µg/mL) was suffixed to the flask and equilibrated for 2 min (Time 2). After that, (4 mL of 2.4×10^{-3} mol/L) CR solution was suffixed to the mixture and diluted to the flask volume with water and stirring well (Time 3). Afterward, the absorbance of the solution was measured at 517 nm.

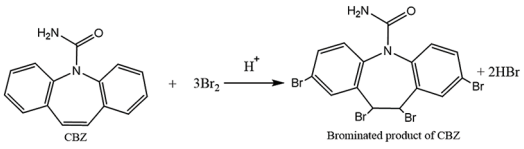
RESULTS AND DISCUSSION

The measure of CBZ in the samples was resolved utilizing the acidified the bromate-bromide blend. We developed two spectrophotometric procedures for the CBZ investigation utilizing bromine as a green brominating agent. Bromine produced by the acid assault on the (bromate-bromide) blend was utilized established on the basis of green chemistry (Anastas and Warner, 1998), which empowers the reserve of the highly toxic and dangerous liquid bromine. The developed methods were eco-friendly, did not form hazardous byproducts, are inexpensive, and easily available. These methods are indirect and established on the extra of excess (bromate-bromide) in and acidic moderate containing the drug. After the reaction is integrate, the unreacted bromine was estimated by reaction with a steady amount of MB or CR. The reaction was monitored by estimating the change in the absorbance of MB or CR at 665 or 517 nm, respectively.

Chemistry

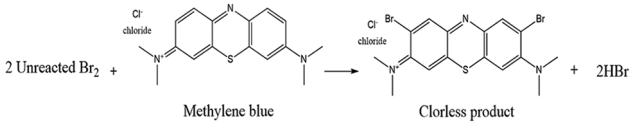
The reaction between CBZ and bromine in an acidic medium involves electrophilic substitution and addition reactions.

$$BrO_3^- + 5Br^- + 6H^+ \longrightarrow 3Br_2 + 3H_2O$$

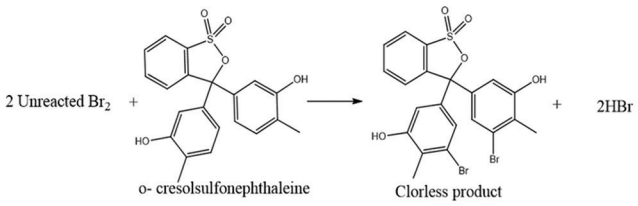


Suggested Mechanism

For method A



For method B



The nitrogen atom appended to the benzene ring as an activating group, allowing for the direct bromination to the para and ortho positions in both rings. Be that as it may, the bromination occurred just at the para positions – due to the steric effects of the amide, minimizing the yield of the ortho-product. The expansion of bromine occurs at the double bond somewhere C3 and C4 in the azepine ring (Mosher, 1992).

Optimization of Reaction Variables

The parameters related to the production of the colored product were individually varied while fixing all others to optimize the reaction conditions.

Effect of Potassium Bromate Concentration

The effect of potassium bromate concentration on the absorbance (MB) of the shaded item was examined between 1.8×10^{-5}–1.5×10^{-4} mol/L [Figure 1a]. It was found that the maximum absorbance of the blue-green product was obtained with 7.5×10^{-5} mol/L potassium bromate. Concentrations higher than this value resulted in decreased absorbance. Therefore, 7.5×10^{-5} mol/L potassium bromate was for subsequent studies. The impact of potassium bromate concentration on the absorbance (CR) of the orange product was studied from 1.8×10^{-5}–1.3×10^{-4} mol/L potassium bromate. The maximum absorbance of the colored product was obtained at a potassium bromate concentration of 9.4×10^{-5} mol/L, above which absorbance decreased [Figure 1b]. Therefore, 9.4×10^{-5} mol/L potassium bromate was utilization for the ensuing work.

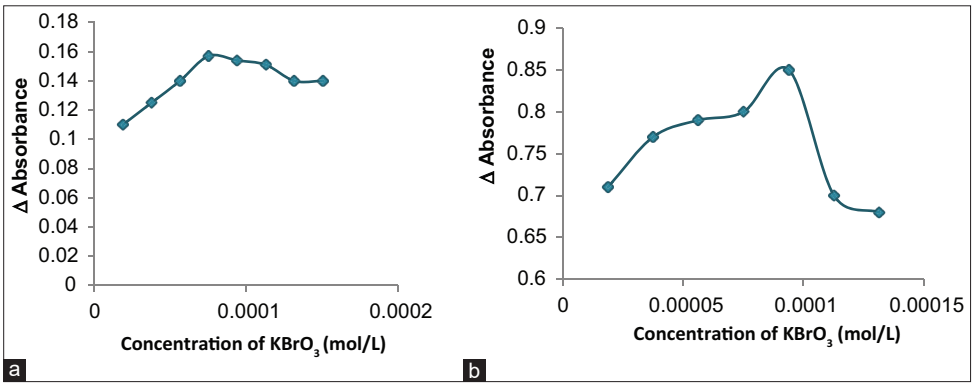


Figure 1: (a) Effect of potassium bromate concentration (b) effect of potassium bromate concentration

Effect of Potassium Bromide Concentration

The study of potassium bromide concentration (MB) showed that the reaction depended on KBr as an oxidizing agent. The absorbance was optimized at 3.7×10^{-4} mol/L KBr, as shown in Figure 2a. Above this concentration, decreased absorbance was observed. The impact of the potassium bromide concentration on the absorbance of the colored product (CR) was investigated between 3.5×10^{-5} and 3.0×10^{-4} mol/L KBr. The optimum value of the absorbance was observed when the concentration

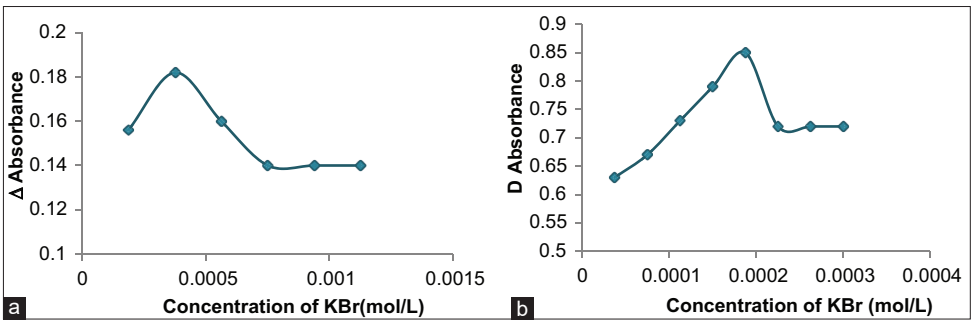


Figure 2: (a) Effect of potassium bromide concentration (b) effect of potassium bromide concentration

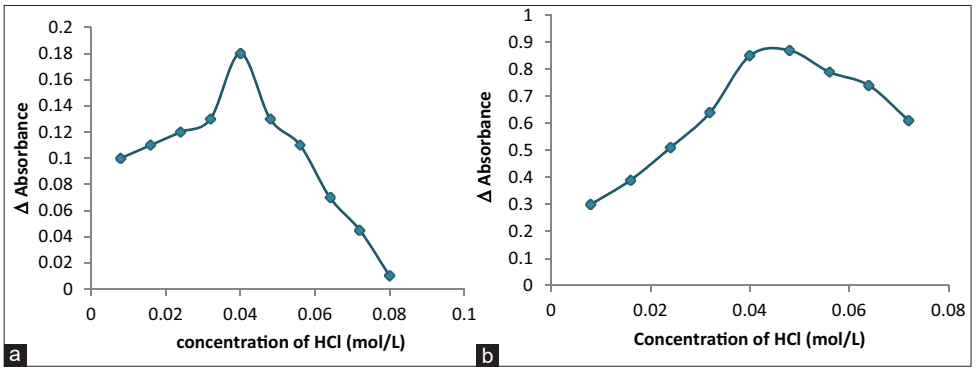


Figure 3: (a) Effect of HCl concentration (b) effect of HCl concentration

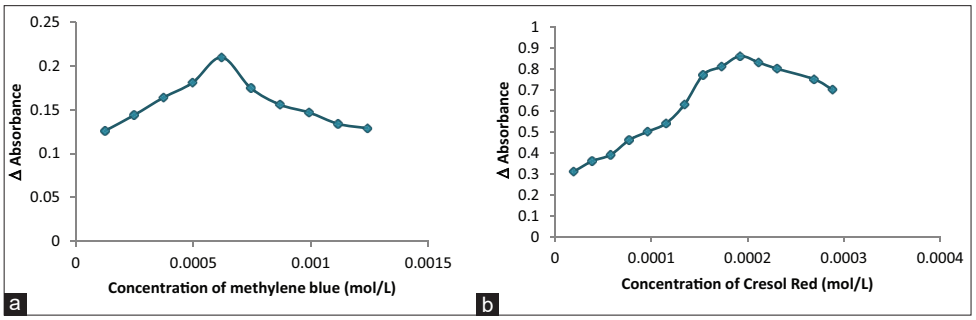


Figure 4: (a) Effect of methylene blue concentration (Method A) (b) effect of cresol red concentration (Method B)

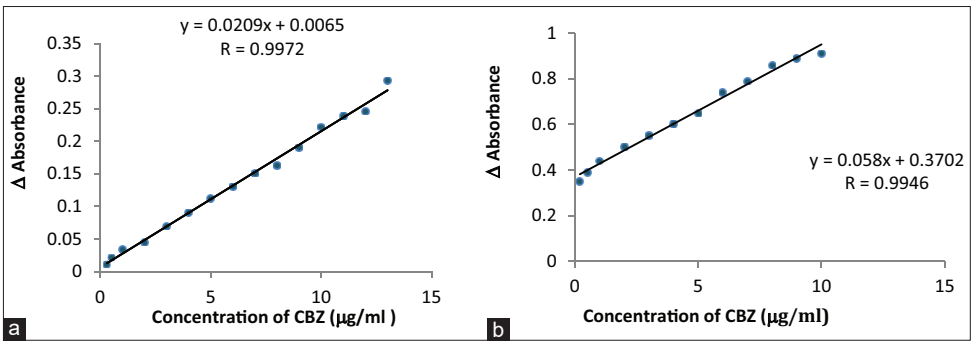


Figure 5: (a) Calibration graph for Method A (b) calibration graph for Method B

Table 1: Effect of mixing time for both methods

Methods	Time	ΔA (Time 1)	ΔA (Time 2)	ΔA (Time 3)
Spectrophotometric (method A)	0.5	0.195	0.179	0.25
	1	0.21	0.185	0.25
	1.5	0.203	0.194	0.25
	2	0.198	0.21	0.25
	2.5	0.189	0.218	0.25
	3	0.181	0.22	0.25
	3.5		0.229	0.25
	4		0.234	0.25
	4.5		0.24	0.25
	5		0.251	0.25
	5.5		0.245	0.25
	6		0.228	0.25
	6.5		0.22	0.25
	7		0.219	0.25
Spectrophotometrc (method B)	0.5	0.78	0.7	0.86
	1	0.86	0.76	0.86
	1.5	0.7	0.81	0.86
	2	0.65	0.863	0.86
	2.5	0.65	0.79	0.86
	3	0.65	0.71	0.86
	3.5		0.67	0.86
	4		0.6	0.86

Table 2: Analytical and regression parameters

Parameter	Method A	Method B
l maximum (nm)	665	517
Molar absorptivity (L/mol/cm)	4938	13703
Limit of detection (μg/mL)	0.315	0.086
Limit of quantification	0.956	0.263
Correlation coefficient (*r*)	0.9972	0.9946

of KBr was 1.8×10^{-4} mol/L [Figure 2b]. Therefore, (1.8×10^{-4} mol/L) KBr used during the subsequent work.

Effect of Hydrochloric Acid Concentration

The influence of HCl on the absorbance of the blue-green product (MB) was investigated at concentrations ranging between 8.0×10^{-3} and 8.0×10^{-2} mol/L. Figure 3a shows that the optimum concentration of HCl was 4.0×10^{-2} mol/L, above which decreased signal was observed. Therefore, 4.0×10^{-2} mol/L HCl was used for the subsequent studies. The impact of hydrochloric acid on the absorbance of the orange product (CR) was investigated in the concentration range between 8.0×10^{-3} and -7.2×10^{-2} mol/L. The absorbance optimized at an HCl concentration of 4.8×10^{-2} mol/L, above which the absorbance decreased, as shown in Figure 3b. Therefore, 4.8×10^{-2} mol/L HCl was used for the subsequent studies.

Effect of MB

The effectiveness of the MB concentration on the absorbance was investigated. The absorbance increased until the MB concentration reached 6.2×10^{-5} mol/L, above which the absorbance decreased, as shown in Figure 4a. Therefore, 7.4×10^{-4} mol/L MB was used for further study.

Effect of CR

The effect of CR concentration on the absorbance of the product was investigated. The absorbance increased when until a concentration of 1.9×10^{-4} mol/L, above which the absorbance decreased, as shown in Figure 4b. Therefore, 1.9×10^{-4} mol/L was used for subsequent work.

Table 3: Intraday and interday precision and accuracy studies

Method	CBZ taken	Intraday (*n*=8)			Interday (*n*=8)		
		CBZ found[a]	Precision[b]	Accuracy[c]	CBZ found[a]	Precision[b]	Accuracy[c]
Spectrophotometric (method A)	1.0	1.025	1.52	2.5	1.03	1.86	3.0
	6.0	5.82	3.46	−3.0	6.05	2.20	0.83
	11	10.88	1.53	−1.09	10.73	1.43	−2.45
Spectrophotometric (method B)	1.0	1.041	3.72	4.1	0.989	4.6	−1.1
	4.0	3.97	5.03	−0.75	4.0	5.10	0.0
	9.0	8.90	2.68	−1.12	8.91	1.63	−1.1

[a]Mean value of n determination, [b]Relative standard deviation %, [c]Error (%) = [(found - taken)/taken] * 100. CBZ: Carbamazepine

Table 4: Determination of CBZ in commercial pharmaceutical formulations with the proposed and the standard methods

Formulation	Product manufacture and country	Labeled amount (mg/tablet)	CBZ found (mg) per tablet			E %MB	E %CR
			Proposed method MB	Proposed method CR	Standard method		
Tables	Carbamazepin (Aristo)	200	7.73	7.79	7.64	1.16	1.92
	Tegrertol (Novartis)	200	7.97	7.89	8.08	−1.38	−2.4
	Carbasam (S.D.I – Iraq)	200	7.81	7.86	7.74	0.89	1.52
	Carbazepin Awa (Awamedica)	200	7.89	7.91	7.82	0.88	1.13
	CBZ (Iranian)	200	7.93	7.96	7.92	0.0012	0.5
	Method A				Method B		
t table = 2.77	t calculated=1.19				t calculated=1.156		
F table = 6.39	F calculated=0.324				F calculated=0.138		

CBZ: Carbamazepine

Physical Optimization

To optimize all conditions for the determination of CBZ by spectrophotometric methods, physical parameters were studied at room temperature, as shown in Table 1.

The reaction can occur at room temperature by an increase or decrease temperature no influence in the reaction rate and absorbance spectra.

Method Validation

Linearity

The calibration graph of the spectrophotometric method used for the quantitative specification of CBZ was obtained, under the optimized reaction conditions [Table 2]. The graph was established by plotting the CBZ concentration in μg/mL against the distinction in absorbance (ΔA). The calibration graph was linear in the concentration range between 0.45 and 15.00 μg/mL [Figure 5a] for method A and 0.50–12.00 μg/mL [Figure 5b] for method B. The analytical and regression parameters are listed in Table 2.

Table 5: Robustness results of method A

Parameters	CBZ (μg/mL)		Found (X±SE; SD)	Recovery (%)	RSD (%)
	Sample	Added			
Wavelength					
660	5	3	(7.996±0.053; 0.092)	99.95	1.15
	5	5	(9.96±0.068; 0.119)	99.6	1.19
670	5	3	(8.096±0.066; 0.115)	101.2	1.42
	5	5	(10.03±0.090; 0.156)	100.3	1.55
Time					
Time 1					
0.5	5	5	(9.951±0.015; 0.027)	99.51	0.27
1.5	5	5	(10.05±0.049; 0.085)	100.5	0.84
Time 2					
4.5	5	5	(9.96±0.0046; 0.008)	99.6	0.08
5.5	5	5	(10.0±0.0310; 0.054)	100	0.54

CBZ: Carbamazepine, SE: Standard error, SD: Standard deviation, RSD: Relative standard deviation

Accuracy and precision

Method precision and accuracy were determined using three equal quantities of the pure CBZ material, and every estimation was performed multiple times (8 times). The relative standard deviation (%) and relative error (%) were estimated for different CBZ groups. The results showed great accuracy and precision. Excellent inter- and intra-day reproducibility was observed, and a progression of analyses was connected for the equivalent diverse convergences of the medication, the estimations were improved the situation bury and intradays with 8 and 5 redundancies separately. Table 3 shows all day-to-day relative standard deviation and relative error values.

Analysis of pharmaceutical preparations

The preferred methods were effectively applied for CBZ assurance in the pharmaceutical formulation (tablet). The outcomes acquired were contrasted to those obtained using the standard techniques (British Pharmacopoeia, 2013) of the Student's t-test for accuracy and f-test for precision [Table 4].

Robustness

Ideally, the detection limit and productivity of the proposed indirect spectrophotometric technique would be unaffected by small variations under measurement conditions encountered during typical utilization. Several method parameters, such as wavelength and time, were varied within a reasonable range, and the quantitative impact of these changes was determined for the pre-analyzed sample solution containing (5.0 μg/mL) CBZ. The results of the robustness tests are shown in Tables 5 and 6, indicating that the proposed technique is robust.

Table 6: Robustness results of method B

Parameters	CBZ (μg/mL)		Found (X±SE; SD)	Recovery (%)	RSD (%)
	Sample	Added			
Wavelength					
510	5	2	(6.973±0.043; 0.075)	99.61	1.07
	5	4	(8.903±0.061; 0.105)	98.92	1.17
525	5	2	(6.933±0.072; 0.125)	99.04	1.80
	5	4	(8.920±0.051; 0.088)	99.11	0.98
Time					
Time 1					
0.5	5	2	(7.063±0.076; 0.133)	100.9	1.88
1.5	5	2	(7.036±0.082; 0.142)	100.5	2.01
Time 2					
4.5	5	2	(6.980±0.061; 0.105)	99.7	1.50
5.5	5	2	(7.043±0.040; 0.070)	100.6	0.99

CBZ: Carbamazepine, SE: Standard error, SD: Standard deviation, RSD: Relative standard deviation

Table 7: Effect of interference of (4 µg/mL) of the drug for the first method (MB)

Interfering species	Conc. µg/ml	Δ Absorbance without interference[a]	Δ Absorbance with interference[a]	E%
Sucrose	4	0.09	0.092	2.22
Titanium dioxide	4	0.09	0.087	–3.33
Lactose	4	0.09	0.091	1.11
Sodium sterate	4	0.09	0.094	4.44
Glucose	4	0.09	0.089	–1.11
Starch	4	0.09	0.093	3.33
Mixture of all	Above concentration	0.09	0.093	3.33

[a]Average of five replication measurement. MB: Methylene blue

Table 8: Effect of interference of (4 µg/mL) of the drug for the second method CR

Interfering species	Conc. µg/ml	Δ Absorbance without interference[a]	Δ Absorbance with interference[a]	E%
Sucrose	4	0.602	0.61	1.328
Titanium dioxide	4	0.602	0.607	0.83
Lactose	4	0.602	0.598	–0.66
Sodium sterate	4	0.602	0.621	3.15
Glucose	4	0.602	0.618	2.657
Starch	4	0.602	0.605	0.498
Mixture of all	Above concentration	0.602	0.625	3.82

CR: Cresol red

Selectivity

To evaluate the effect of interference, the effects of impurities were examined for CBZ determination. The selection of interferences compounds was performed according to the composition of the drug samples. The influence of the presence of common additives such as magnesium stearate-, lactose, titanium dioxide-, starch-, sucrose, and glucose- was tested, and the results are shown in Tables 7 and 8 for methods A and B.

CONCLUSION

Estimation of CBZ by indirect procedure has been attempted. In the optimization of different parameters for the proposed methods, the concentration of all components was taken into account; optimum conditions were considered to be those affording maximum intensity, greatest possible signal stability, and maximum linearity. The reaction can be carried out at room temperature and the sample preparation is minimal, no pretreatment is required, and the analysis is simple, accurate, and precise. The cost of chemical standard and reagents are minimal (since no large amount of expensive reagents was consumed). The detection limit data indicated that the microgram quantity of CBZ can be accurately determined.

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