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Indirect Spectrophotometric Estimation of Carvedilol via Oxidation and Bleaching of Eriochrome Black-T Color in Bulk Drug and Pharmaceutical Preparations

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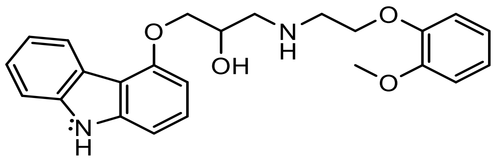
ABSTRACT

Carvedilol (CAR) has been estimated by the indirect spectrophotometric method. The suggested method was based on the oxidation of CAR with an excess of potassium per- iodate (KIO_4) in the presence of hydrochloric acid, then the unreacted or the excess KIO_4 was bleaching the color of Eriochrome black-T dye (EBT), the absorbance of unreacted EBT has been estimated at wavelength 520 nm (the maximum absorption of EBT). The measured absorbance is directly proportional to the amount of CAR in the solution. All parameters affected of by the oxidation of CAR and bleaching of EBT color have been studied and the optimum conditions have been fixed. The linearity of the method is in the range (0.5 -15.0) µg.ml-1, the molar 10^4 $l.mol^{-1}.cm^{-1}$, 1.1340×absorptivity value is equal to and the Sandell's index value for sensitivity is equal to $µg.cm^{-2}$. The limit of detection (LOD) was 0.0358 0203µg $.ml^{-1}$, and the limit of quantitation (LOQ) was .0 0693 µg $.ml^{-1}$. The suggested method has been applied .0 for the determination of CAR in pharmaceutical formulations with good recovery and precision.

Keywords: Spectrophotometric determination, Eriochrome black-T, Bleaching color, Carvedilol.

INTRODUCTION

Carvedilol (CAR), (±)-1-(carbazol-4-yloxy)-3-[(2-0-methoxyphenoxy) ethyl)amino)-2-proanol, is a noncardio-selective B-blocker Fig. (1).



$C_{24}H_{26}N_2O_4$, M.Wt. = 406.47 g/mol.

Fig. 1: Chemical formula and structure of CAR.

CAR is used in hypertension and angina pectoris and as an adjunct to standard therapy in symptomatic heart failure, it is also used to reduce mortality in patients with left ventricular dysfunction after myocardial infarction (Sweetmns, 2009). Carvedilol has been studied and determined by several analytical methods, such as, reverse-phase high-performance liquid chromatography (RP-HPLC) (Mahajan *et al.,* 2021), LC–MS/MS gradient elution (Joubert *et al.*, 2022) and spectroscopy methods (UV, ratio derivative, first derivation ratio, ratio derivative subtraction methods (Chanduluru and Sugumaran, 2022). Carvedilol has been determined using proton-transition reaction through the complex formation (Ibrahim *et al.,* 2014), also has been determined using charge transfer complex formation with iodine, and ion pair complex (Cardoso *et al.,* 2007), or through the ion-pair complex with Eriochrome black-T in an acidic media (pH2) (Mzban *et al.,* 2020), the indirect method by oxidation and bleaching color of methyl orange dye by Ce(IV) sulphate as oxidant agent has been developed (Shehab and Mohammed, 2021), Schiff 's base reaction with 4-hydroxybenzaldehyde also has been used (Alallaf *et al.,* 2022), oxidative coupling method by phenothiazine, in presence of potassium dichromate (Mohammed *et al.,* 2022), determination and kinetic study carvedilol via charge transfer complex formation has been established (Ahmed *et al.,* 2022). Direct voltammetric oxidation of CAR (Yilmaz and Kaban, 2014), also has been determined by electrochemical oxidation of carvedilol at platinum electrode in acetonitrile solution containing 0.1MTBAClO_4 for determination of CAR in non-aqueous media (Yilmaz and Ekinci, 2011).

EXPERIMENTAL

Apparatus

Spectral measurements and absorbance readings were carried out using a JASCOV-630 spectrometer, and glass cells with a light path of 1 cm were used. The acidity of the solutions was measured using TRANCE BP3001 professional pH meter.

Chemicals used and prepared solutions

All chemical agents and solvents used in the present work are of analytical grade.

Carvedilol solution, 100 µg. ml^{-1}:

This solution was prepared by dissolving 0.0100 g of CAR in 20 ml of methanol (US Pharmacopoeia. 2021), shaking and then the volume was completed to the mark of 100 ml volumetric flask with methanol.

Potassium periodate (KIO_4) solution, 1×10^{-3} M:

This solution was prepared by dissolving 0.0230 g of KIO_4 in a small amount of distilled water and then completing the volume to 100 ml with distilled water in a volumetric flask.

Eriochrome black -T (EBT) solution, 0.1%:

This solution was prepared by dissolving 0.1000 g of EBT dye in 100 ml of distilled water in a 100 ml volumetric flask

Hydrochloric acid solution, a proximally 1.0M:

8.4 ml of concentrated hydrochloric acid was diluted to100 ml with distilled water in a volumetric flask.

Pharmaceutical solutions, 100 µg.ml^{-1}:

Carve Tablets produced, TAD Pharma / GmbH. German company

Solution of the pharmaceutical preparation Carve tablets produced by German company TAD Pharma/ GmbH. (Each tablet contains 12.5 mg of CAR). The average weight of 10 tablets is 122.6 mg. After grinding and mixing well, the weight equivalent to 0.0100 g of pure CAR from the powder was taken and 20 ml of methanol was added with shaking well and then diluted the volume up to 100 ml with distilled water and then filter using filter paper No1.

Alphabeta pills produced by the Swiss company (Hoffmann-La Roche):

The solution of tablet Alphabeta pills (Swiss company, Hoffmann-La Roche). Each tablet contains 6.25 mg of CAR. The average weight for 10 tablets was 121.0 mg, after grinding and mixing them well, weighing the equivalent amount to 0.0100 g of pure CAR and adding 20 ml of methanol with good shaking of the solution and completing the volume to 100 ml with distilled water and then filtering it using filter paper No. 1.

Procedure and calibration curve:

The calibration curve for the suggested method was prepared by adding various volumes of CAR (100µg.ml^{-1}) to cover the range of CAR concentration from 0.5 -15.0 µg.ml^{-1} in a series of 10 ml volumetric flasks, then 1.5 ml of KIO4 and 1.25ml of 1.0M HCl were added and after a period waiting for 15 min., 0.5 ml of EBT solution was added and left the flasks for 10 min. at laboratory temperature. Then the volume is completed to the mark with DW. The absorbance of solutions was measured at the wavelength 520 nm as shown in Fig. (2).

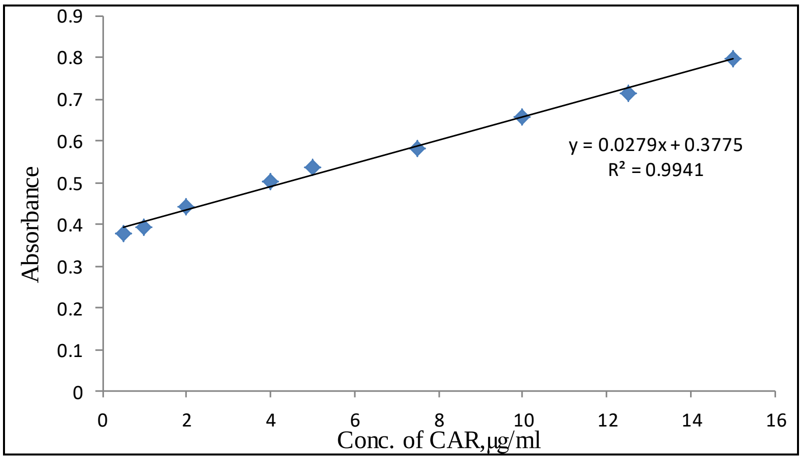


Fig. 2: Calibration curve of CAR.

Fig. (2) shows that the linearity of estimation CAR via the suggested method was from 0.5 - 15.0 µg.ml^{-1}, and the molar absorptivity and the Sandell's index values are calculated and equal to 1.1340×10^4 l.mol^{-1}.cm^{-1} and to 0.0358 µg.cm^{-2} respectively.

RESULTS AND DISCUSSION

Principle of the method:

The first step of the proposed method is based on the oxidation of CAR by adding a fixed amount of KIO_4 in an acidic medium and leaving it for a period of time for the completion of the oxidation of CAR. Then the unreacted KIO_4 was oxidized a known amount of EBT, and the absorbance was measured at 522 nm. The decrease of KIO_4 concentration upon using it in the oxidation of known concentration of drug leads to an increase in the absorbance of EBT at 520 nm, which depends on the CAR concentration. The discoloration was caused by the destruction of the dye with KIO_4 Fig. (3). The increasing concentration of CAR leads to a decrease in the concentration of KIO_4 for bleaching EBT and leads to an increase in the absorbance at 520 nm which is proportional to CAR concentration.

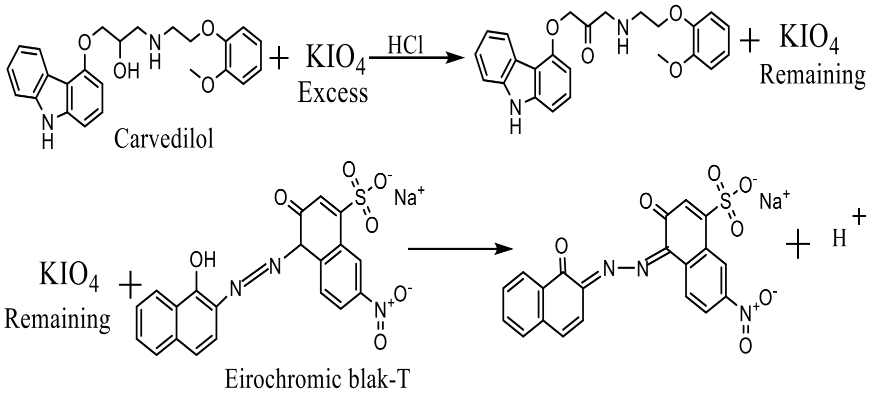


Fig. 3: Proposed mechanism for the oxidation of CAR and bleaching color of EBT by KIO_4

Spectrum of EBT

The dye spectrum was taken to determine the maximum wavelength (λmax) that will be used in subsequent measurements by taking 0.5 ml of the EBT solution and adding 0.1 ml of 1.0 M HCl the volume was completed with distilled water to 10 ml and the spectrum against the blank solution has been taken Fig. (4).

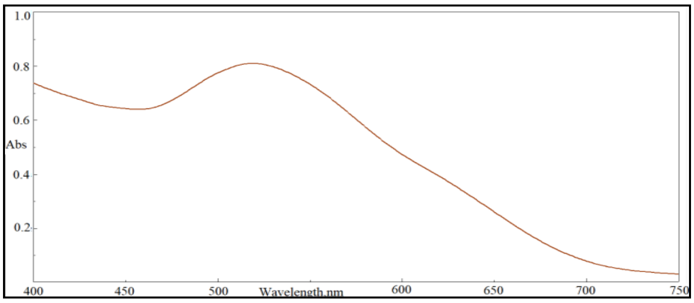


Fig. 4: Absorption spectrum of EBT.

Fig. (4) shows the highest absorption of EBT at a wavelength of 520 nm, thus it was recommended in the subsequent experiments.

Optimization of conditions:

To establish the experimental conditions for the high sensitivity of the method, the effect of various parameters such as oxidizing agent, and time were studied and optimized.

Effect of EBT amounts

Solutions prepared from various amounts of EBT were used in the construction of the standard curve of EBT, and their absorbance was measured at the wavelength 520nm, as shown in Fig. (5).

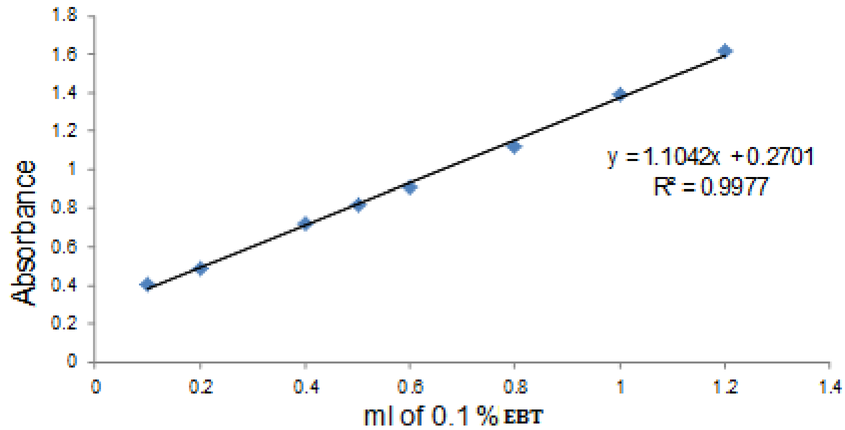


Fig. 5: The calibration curve of EBT

Through the results in Fig. (5), 0.5 ml was chosen because it falls within the linearity of the calibration curve of the EBT dye and gives it good absorbance (0.822), so it is adopted in subsequent experiments.

Effect of the type of oxidizing agent:

The effect of the various types of oxidizing agents was studied by preparing three solutions of oxidizing agents, potassium periodate (KIO_4), N-bromosucinimide (NBS), and N-chlorosucinamide (NCS) at a concentration of 0.01 M for each one. Several volumetric flasks of 10 ml were taken and 0.5 ml of EBT dye and 1.0 ml of 1.0 M HCl to each flask were added and 1 ml of each oxidizing agent was added and the absorption drawing of the solutions versus their blank solutions have been done at a range of wavelength from 400-700 and the results were as in the Fig. (6) and in (Table 1).

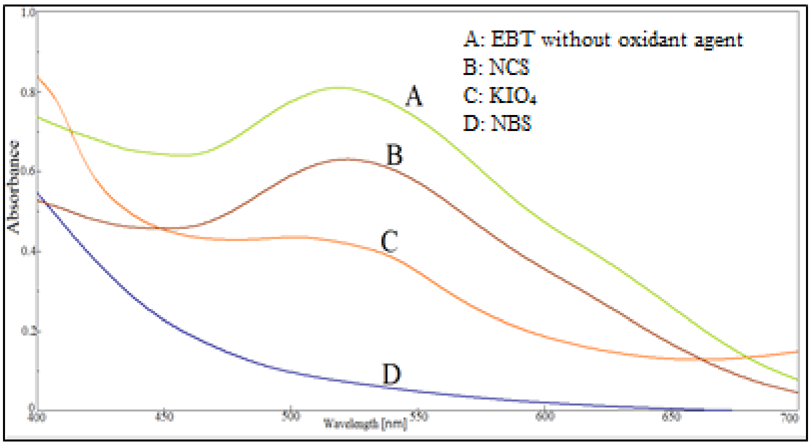


Fig. 6: Absorption spectrums of the EBT dye after adding different oxidizing agents

Table 1: Effect of the type of oxidizing agent on the absorbance of the dye

Typed of oxidant reagent (0.01M)	Absorbance
NBS	0.0752
NCS	0.627
KIO_4	0.308
Without oxidant agent	0.842

Through the results shown in Fig. (5) and (Table 1), NBS gave the highest oxidation potential (maximum bleaching), but it was not chosen as an oxidizing agent because in high concentrations of CAR it causes turbidity of solutions, KIO_4 was chosen as an oxidizing agent in subsequent experiments.

The optimal amount of KIO_4

Several 10 ml volumetric flasks were taken and 2.5-12.5 µg.ml^{-1} CAR was added to each of them 1.0 ml of 1.0 M hydrochloric acid followed by different amounts of KIO_4 (0.1-2) ml were added. The flasks were left for 10 min. at laboratory temperature with shaking, then 0.5 ml of EBT solution was added to each, shaken well, waited for five min., and completed the volume with distilled water. The absorbance was measured versus corresponding blank solution at 520 nm and the results were as in the (Table 2).

Table 2: Effect of oxidizing agent amount on the absorbance of ERO-T dye with CAR

KIO_4 0.01 M, ml	Absorbance µg. of CAR/ml					R^2
	2.5	5	7.5	10	12.5	
0.1	0.748	0.774	0.799	0.802	0.806	0.8594
0.25	0.734	0.757	0.793	0.794	0.804	0.8890
0.5	0.709	0.739	0.759	0.786	0.789	0.9532
0.75	0.585	0.606	0.618	0.651	0.686	0.9655
1.0	0.483	0.571	0.580	0.624	0.692	0.9452
1.5	**0.334**	**0.394**	**0.468**	**0.568**	**0.583**	**0.9681**
2.0	0.337	0.409	0.430	0.495	0.589	0.9622

The results in (Table 2), indicated that the volume of 1.0 ml of KIO_4 is not sufficient to cover the added range of amount of CAR and does not give the higher value of determination coefficient (R2) at 1.5 ml of KIO_4, it was decided to adopt this volume in subsequent experiments.

Effect of acid type:

The effect of different types of acids was studied to obtain the highest absorbance value by preparing several samples, each containing 1.0 ml of CAR (100 µg.ml-1) with 1.0 ml of 1.0 M various acids, then 1.5 ml of 0.01 M oxidizing agent, after a good shake, wait for 10 minutes, then add 0.5 ml of EBT to each of this flask, wait for 5 minutes, and complete the volumes with distilled water to the mark and measure the absorbance against the blank solution and the results were as in the (Table 3).

Table 3: The results of the use of different acids on absorption

Acid (1M)	Absorbance	λ_{max} (nm)	pH
HCl	**0.569**	**520**	**1.53**
H_2SO_4	0.542	526	1.42
HNO_3	0.515	522	1.50
CH_3COOH	0.439	517	2.05

The results in Table 3 show that hydrochloric acid was the optimal acid, it gives the highest absorbance and thus it was chosen in subsequent experiments. Also, the optimal amount of HCl has been studied (Table 4).

Table 4: Selection of the optimal amount of hydrochloric acid

ml of HCl (1M).	Absorbance	pH
0.5	0.505	1.84
1.0	0.563	1.62
1.25	**0.574**	**1.57**
1.5	0.572	1.48

From the absorbance values for the remaining dye in (Table 4) 1.25 ml of 1.0 M HCl have the highest absorbance, so it was selected for subsequent experiments.

Effect of time required for CAR oxidation and bleaching the EBT color

1 ml of CAR (100 µg ml^{-1}) was added to a series of 10 ml volumetric flask,1.5 ml of oxidizing agent KIO_4, and 1.25 ml of 1.0 M HCl were added, then the solutions were left for different times to complete the oxidation process, then 0.5 ml of EBT was added. and the solutions were left for different periods to complete the process of bleaching the dye with the remaining amount of the oxidizing agent, after dilution to the mark the absorbance of the solutions was measured against its blank solution and the results are listed in (Table 5).

Table 5: Effect of oxidation time and bleaching time on absorbance.

Time, min after addition of KIO_4	Absorbance, standing time after addition of EBT, min.					
	Immediate	5	10	15	20	25
Immediate	0.571	0.574	0.572	0.580	0.579	0.587
5	0.580	0.589	0.601	0.584	0.582	0.581
10	0.609	0.613	0.630	0.628	0.625	0.602
15	0.610	0.639	**0.665**	0.663	0.663	0.662
20	0.612	0.661	0.657	0.650	0.650	0.648
25	0.613	0.664	0.637	0.632	0.632	0.631

Through the results in the (Table 5), a waiting time of 15 min. was adopted after adding the oxidizing agent, and also 10 min. after adding the EBT before diluting with D.W. then the absorbance measured at 520 nm.

Study the sequence of addition:

The effect of different sequences of additives of solution components was studied and the results as shown in the (Table 6).

Table 6: Effect of order addition

	Order of additions	Absorbance
I.	CAR + HCl + KIO_4 + EBT	0.638
II	**CAR + KIO_4 + HCl + EBT**	**0.649**
III	CAR + KIO_4 + EBT + HCl	0.611
IV	CAR + HCl + EBT + KIO_4	0.594

The results in (Table 6) show that the order from I to III have approximately the same absorbance and order IV, a decrease in the absorbance value occurred due to the competition between CAR and the EBT on oxidation with the oxidizing agent KIO_4, therefore the order number II was recommended in the next experiments.

Study the effect of different solvents:

Various types of solvents used in dilution were studied to choose the most appropriate ones. The results were as shown in Fig. (7) and (Table 7).

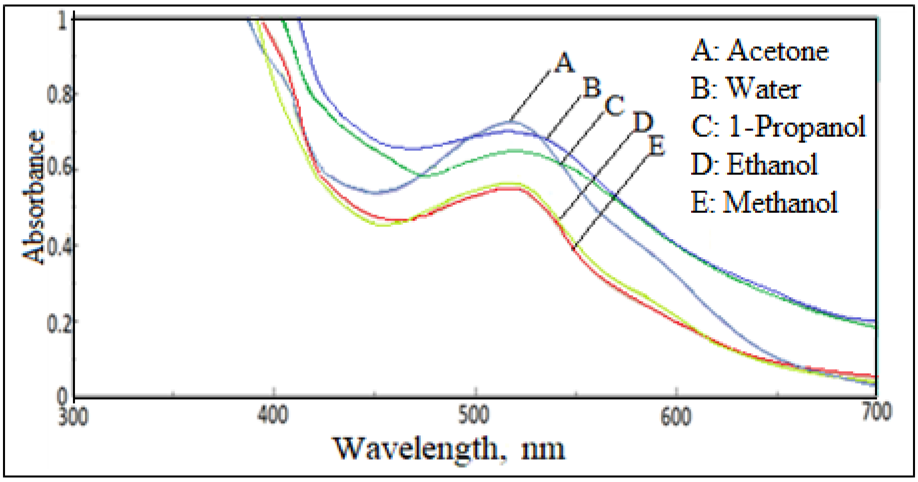


Fig. 7: Absorption spectra for 10 µg of CAR using different solvents.

Table 7: Effect of solvents on absorbance and molar absorption coefficient

Solvent	Absorbance	λ_{max} (nm)	ε: $l.mol^{-1}.cm^{-1}$
Ethanol	0.5599	516	2.2758×10^4
Methanol	0.5426	516	2.2055×10^4
Acetone	0.6967	517	2.8318×10^4
1-Proponal	0.6304	521	2.5623×10^4
Water	0.6704	520	2.7248×10^4

The results in Fig. (6) and (Table 8) show that the highest absorption was when using acetone in dilution, according to the advantages of distilled water (ease of use, safety, and etc...), so its use was maintained in subsequent experiments.

Study the effect of time on stability:

The stability of the unreacted EBT was studied and the results illustrated in (Table 8).

Table 8: The stability of unreacted EBT

Time min.	Absorbance/ µg of CAR	
	5	10
Immediate	0.5632	0.6682
5	0.5394	0.6607
10	0.5384	0.6594
15	0.5320	0.6581
20	0.5298	0.6583
30	0.5294	0.6554
35	0.5295	0.6551
40	0.5287	0.6550
45	0.5285	0.6554
50	0.5285	0.6551
55	0.5280	0.6550
60	0.5275	0.6548

Through the results shown in (Table 8) it is clear that the residual EBT is stable for not less than 60 minutes.

The optimum condition obtained through previous experiments are listed in (Table 9).

Table 9: The optimal conditions of the suggested method

Parameter	Optimum condition
Maximum wavelength of EBT, nm.	520
Oxidizing agent	KIO_4
Amount of KIO_4, ml	1.5
Acid type, Conc.	HCl, 1.0M
Amount of HCl, ml	1.25
Amount of EBT, ml	0.5
Time of oxidation, min	15
Time of bleaching min.	10
Stability, min.	60

(Tablet 10) included the optical characteristic of the suggested method.

Table 10: Optical characteristic and statistical of the regression equation

Analytical parameters	Present method
Type of reaction	Decolorization dye
Oxidation agent	KIO_4
Dye	EBT
pH	Acidic medium
Temperature (℃)	RT
λ_{max}. nm	520
Medium of reaction	Aqueous
Linear range ($\mu g.ml^{-1}$)	0.5 -15.0
Slope	0.0279
Regression equation	$y = 0.0279x + 0.3775$
Determination coefficient	0.9941
Molar absorptivity ($l.\ mol^{-1}.\ cm^{-1}$)	1.1340×10^4
Sandell 's sensitivity $\mu g.cm^{-2}$	0.0358
LOD $\mu g.ml^{-1}$	.00207
LOQ $\mu g.ml^{-1}$	.00693
RSD%, n=5	1.0227
Calculated t-value for Carve 12.5mg/tab.	0.2306

Applications of the proposed method to pharmaceutical preparations:

The proposed method for estimating CAR was applied to three different concentrations of Carve grains and Alpha-beta grains prepared previously and the results are fixed in (Table 11).

Table 11: Application of the proposed method in the estimation of CAR in pharmaceuticals preparations

Drug.	µg CAR Present	µg CAR measured	Recovery %	Drug contain, (mg)
Alphabeta 6.25mg/tab Hoffmann-La Roche	2.5	2.49	99.60	6.22
	5	4.92	98.40	6.15
	10	9.68	96.80	6.05
Carve, TAD 12.5mg/tab GmbH, Germany	2.5	2.49	99.60	12.45
	5	4.89	97.80	12.22
	10	9.93	99.30	12.41

Accuracy and precision

The accuracy of the proposed CAR estimation method was calculated and according to the working method adopted in finding the standard curve for three different concentrations of 2.5, 5.0, and 10.0 µg/ml of CAR, each of which has five readings of the relative error (RE) and relative standard deviation (RSD) were calculated to determine the compatibility of the method. Results as in (Table 12).

Table 12: Accuracy and precision of the method

Sample	Amount taken, µg	RE %	RSD%
Alphabeta 6.25 mg/tab Hoffmann-La Roche	2.5	-0.050	1.2093
	5	−0.014	1.2535
	10	−0.031	0.6054
Carve TAD 12.5mg/tab. GmbH, Germany	2.5	0.396	0.4987
	5	−2.200	1.6399
	10	−6.606	3.8042

The results in (Table 12) indicated that the method has good accuracy and precision.

Application using the standard addition method:

The proposed method was applied for the determination of CAR in a solution of 100 µg. ml^{-1} for Carve tablets containing 12.5 mg by preparing two series of volumetric flasks of 10 ml capacity. The first series of flasks containing a fixed concentration of 2.5 µg.ml^{-1} of the above-prepared solution and add different volumes of a standard solution of CAR (100 µg.ml^{-1}) ranging from 0 to 0.5 ml, whereas the second series containing a fixed concentration of 5.0 µg.ml^{-1} of Carve tablets, followed by the same amounts of solutions in the first series, then complete the method according to the optimal conditions fixed in (Table 10), The results showed in the Fig. (8) and (Table 13).

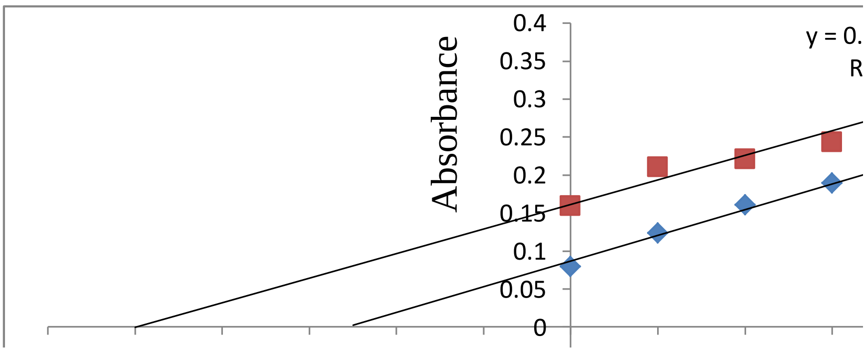


Fig. 8: Standard addition curves for determination of CAR in Carve tab

Table 13: Application of the standard additions method and finding the percentage of recoveries

Drug,	µg CAR taken	µg CAR measured	Recovery %	RE%	RSD%	Drug, contain mg/Tab.
Carve, 12.5 mg/tab, GmbH, Germany	2.5	2.56	102. 4	2.40	0.696	12.82
	5.0	4.96	99. 2	-0.61	0.151	12.41

The comparison of the suggested method

The method comparison was based on the t-test to find out the degree of congruence between the current method and the standard method adopted in the British Pharmacopoeia using RP-HPLC, with mobile phase methanol: orthophosphoric acid 50:50 and C_{18} column was used, and detected at 285nm) (British Pharmacopoeia, 2022) and to determine the validity of the current method in application to pharmaceutical preparations by calculating the percentages of recoveries of five samples of the solutions of pharmaceutical preparations under study containing 10 µg.ml^{-1} of CAR using the proposed method and the standard method established in the British Pharmacopoeia (Table 14).

Table 14: Comparison of the proposed method for the estimation of CAR with the standard method

Drug, mg/tab	Recovery %		t. exp*
	Present method	Standard method British Pharmacopeia,2022	
Carve 12.5mg/tab. GmbH, Germany	98.58	100.02	0.2306
ALPHABETA 6.25mg/tab. Hoffmann-La Roche	99.8	99.42	0.1605

*Average of five determinations of 100 µg CAR.

The calculated t-values are less than the tabular t-values for eight degrees of freedom and at a confidence level of 95%, which indicates that there is no significant difference for the two measurement methods.

CONCLUSION

The present method included a sensitive, simple, and accurate spectrophotometric method for the estimation of CAR as pure and in formulations via oxidation with KIO_4 in an acidic medium and the excess amount of KIO_4 used in bleaching the color of EBT dye. The maximum absorption of EBT, or wavelength 520 nm, has been estimated to represent the absorbance of unreacted EBT. The quantity of CAR in the solution is directly correlated with the observed absorbance. With good recovery and precision, the proposed approach has been used to determine CAR in pharmaceutical formulations.

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التقدير الطيفي غير المباشر للكارفيديلول بشكله الحر وفي مستحضراته الصيدلانية باستخدام الاكسدة وقصر لون صبغة الأيروكرم الاسود – تي

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الملخص

تتضمن الطريقة المقترحة طريقة طيفية غير مباشرة لتقدير الكارفيديلول في الوسط المائي تعتمد الطريقة على أكسدة الكارفيديلول مع زيادة من العامل المؤكسد بيرويودات البوتاسيوم وبوجود وسط حامضي من حامض الهيدروكلوريك المخفف، والكمية الفائضة من العامل المؤكسد تعمل على قصر لون صبغة الأيروكرم الاسود –T والمضافة الى وسط التفاعل ويتم قياس شدة لون للصبغة المتبقية عند الطول الموجي الأعظم 520 نانوميتر، ويتناسب الامتصاص طردياً مع كمية الكارفيديلول وبعد دراسة الظروف المثُلى كان مدى التركيز للمنحني القياسي ضمن المدى (0.5–15.0) مايكروغرام/ مللتر وكان معامل الامتصاص المولاري 1.1340×10^4 لتر. مول$^{-1}$. سم$^{-1}$ وحساسية ساندل 0.0358 مايكروغرام. سم$^{-2}$، و كانت قيم LOD و LOQ (0.0207 و 0.0693) مايكروغرام/ مللتر على التوالي، طُبقت الطريقة بنجاح في تقدير الكارفيديلول في المستحضرات الصيدلانية (أقراص) وبنسب استرجاعية وضبط جيدين.

الكلمات الدالة: قياس الطيف الضوئي، الأيروكرم الاسود –T، قصر اللون، كارفيديلول.