

# A Highly Sensitive Kinetic-Spectrophotometric Method for the Assay of Carbamazepine in Pure and Commercial Tablet

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## Abstract

The study aimed to recommend a new spectrophotometric-kinetic method for determination of carbamazepine (CABZ) in its pure form and pharmaceutical forms. The proposed procedure based on the coupling of CABZ with diazotized sulfanilic acid in basic medium to yield a colored azo dye. Factors affecting the reaction yield were studied and the conditions were optimized. The colored product was followed spectrophotometrically via monitoring its absorbance at 396 nm. Under the optimized conditions, two method (the initial rate and fixed time (10 minute)) were applied for constructing the calibration graphs. The graphs were linear in concentration ranges 2.0 to 18.0  $\mu\text{g}\cdot\text{mL}^{-1}$  for both methods. The proposed was applied successfully in the determination of CABZ in its commercial formulations.

**Keywords:** Kinetic, Spectrophotometry, Carbamazepine, Pharmaceutical formulations.

## طريقة طيفية حركية ذات حساسية عالية لتقدير عقار الكاربامازيبين بصورته النقية وفي المستحضرات الصيدلانية

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## الخلاصة

يهدف البحث الى تطوير طريقة طيفية حركية لتقدير عقار كاربامازيبين بصورته النقية وفي مستحضراته الدوائية. تعتمد هذه الطريقة على ازدواج عقار الكاربامازيبين مع الكاشف حامض سلفانيليك المؤزوت في وسط قاعدي. حيث تم دراسة العوامل التي تؤثر على التفاعل وتثبيت الظروف المثلى، ويصاحب التفاعل الطيفي قياس معدل التغير في الامتصاصية عند طول الموجي ٣٩٦ نانومتر، وعند الظروف المثلى تم دراسة حركية التفاعل وإيجاد منحنى المعايرة من خلال طريقتي معدل السرعة والزمن الثابت عند ١٠ دقائق، وكانت حدود التراكيز بين ٢.٠-١٨.٠ مكغم. مل<sup>-١</sup>. وقد تم تطبيق الطريقة بنجاح لتقدير عقار الكاربامازيبين في مستحضراته الدوائية. الكلمات المفتاحية: حركية، التقدير الطيفي، كاربامازيبين، المستحضرات الصيدلانية.

## Introduction

Carbamazepine (CABZ), is anticonvulsant drug, chemically it is 5-H-dibenz (*b, f*) azepine-5-carboxamide<sup>(1)</sup> Figure (1). Carbamazepine is widely used as an anticonvulsant and antiepileptic drug<sup>(2)</sup>. It may be used in schizophrenia along with other medications and as a second line agent in bipolar disorder<sup>(3)</sup>.

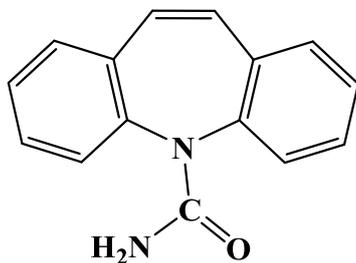


Figure (1): Chemical structure of carbamazepine.

Several methods such as HPLC<sup>(4)</sup>, GC-MS<sup>(5)</sup>, voltammetric<sup>(6)</sup>, spectrophotometric<sup>(7, 8)</sup>, have been developed for determination of CABZ in pharmaceutical preparations. According to a relative small number of kinetic methods for quantitative determination of CABZ have been reported in the literature, the work was done to develop a new sensitive, selective, and free of interference kinetic - spectrophotometric procedure by coupling CABZ with the diazotized sulfanilic acid.

## Experimental

### Apparatus

All spectrophotometric measurements were performed using Shimadzu 1800 UV-Visible, with 1 cm silica cells. A Sartorius BL 210S balance, water bath (Memmert W-200 RING- Germany) and hot plate with magnetic stirrer (Germany).

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## Materials and Methods

### Materials

Carbamazepine standard powder was obtained, as a gift, from the State Company for Drug Industries and Medical Appliances, Samara-Iraq (SDI). Acetic acid was supplied from BDH while sulfanilic acid and sodium hydroxide were supplied from Riedel-de Haën and Barcelona-Espana respectively. Taver (Cyprus), Tegral (Egypt), and Tegratol (Switzerland) tablets labeled to contain 200 mg of CABZ per tablet was purchased from commercial source.

### Method

#### Preparation of solutions for standards and reagents

Stock and working standard solutions:

A 0.25g of carbamazepine is dissolved in 10 mL of concentrated  $\text{CH}_3\text{COOH}$  and leaved to stand for 10 minutes. The volume is then completed with ( $\text{CH}_3\text{COOH}:\text{H}_2\text{O}$  1:1 (V/V) solution) to 250mL in a volumetric flask to give a concentration of ( $1000 \mu\text{g}\cdot\text{mL}^{-1}$ ). This stock solution was used to prepare more dilute working solutions (2.0, 4.0, 6.0, 8.0 10.0, 13.0, 15.0, and  $18.0 \mu\text{g}\cdot\text{mL}^{-1}$ ).

#### Diazotized sulfanilic acid solution<sup>(9, 10)</sup> (0.01M)

0.2 g of sulfanilic acid was dissolved in 30 mL distilled water, with continuous stirring and heating until complete dissolution. Then 1.7 mL of 11.8M HCl is added with continuous stirring, and the mixture is transferred into a brown 100 mL volumetric flask, cooled to 0 - 5 °C in ice-bath. After then 0.069g of  $\text{NaNO}_2$  is added and the mixture is stirred vigorously. Five minutes later, the solution is made up to final volume with cold water. The solution is stable for at least 48 hours when is stored in a refrigerator.

#### Sodium hydroxide solution (~ 5M)

20 g of the base was dissolved in 50 mL of distilled water (DW). The solution was then diluted to 100 mL with DW.

#### Solution for the analysis of carbamazepine in formula preparation

An equivalent weight to one tablet (0.025081g, 0.027253g, and 0.026772g) was taken from the fine powder of 10-tablets of Taver, Tegral, and Tegratol respectively and dissolved in 4 mL of concentrated acetic acid with stirring for 10 minutes. The solution was let to stand for another 10 minutes, then its volume was completed to 100 mL with ( $\text{CH}_3\text{COOH}:\text{H}_2\text{O}$  1:1 (v/v)) to obtain  $200 \mu\text{g}\cdot\text{mL}^{-1}$  CABZ. The undissolved materials were filtered-off via Whatman filter paper No.41 before use.

## Results and discussion

### Absorption spectra

Absorption spectrum for the azo dye product formed upon the reaction between the diazotized sulfanilic acid and CABZ in alkaline medium was recorded, against the reagent blank, under primary testing conditions (1mL of 0.01M diazonium salt, 5 minutes at 60 °C and 3 mL of 5M NaOH). Figure (2) shows that the maximum absorption of the yellow dye under primary conditions is located at 402.0 nm at which the reagent blank shows a negligible absorption.

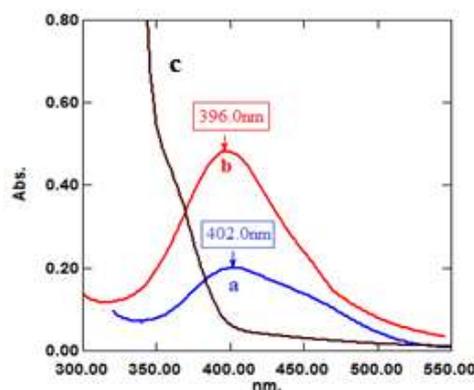


Figure (2): Absorption spectra of: (a) Reaction product of  $10 \mu\text{g}\cdot\text{mL}^{-1}$  CABZ vs reagent blank, under primary test. (b) Reaction product of  $10 \mu\text{g}\cdot\text{mL}^{-1}$  CABZ vs reagent blank, under the optimum conditions.(c)Blank solution against distilled water.

### Optimization of experimental variables

The effects of various parameters related to the formation of the yellow azo dye have been studied to optimize their values.

#### Volume of diazonium salt solution

Different volumes (0.5–2.0 mL) of 0.01 M diazotized sulfanilic acid solution were used to carry out the reaction. The results show that 1.25 mL of this solution was sufficient for the production of maximum and reproducible color intensity Figure (3).

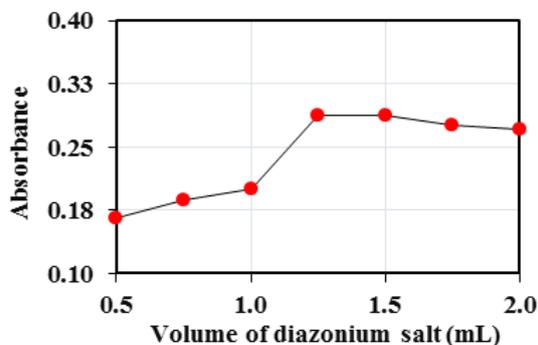


Figure (3): Effect of diazonium salt volume.

**Reaction temperature**

Different temperatures (25-100 °C) were examined to investigate their effect on the progress of the coupling reaction. It was observed that the value of the measured absorbance of the reaction product continued to increase up to 80 °C, while higher temperatures lead to depression in its value. This probably due to the dissociation of azo-dye therefore, all the coupling reactions were performed at 80 °C<sup>(11,12)</sup>, Figure (4).

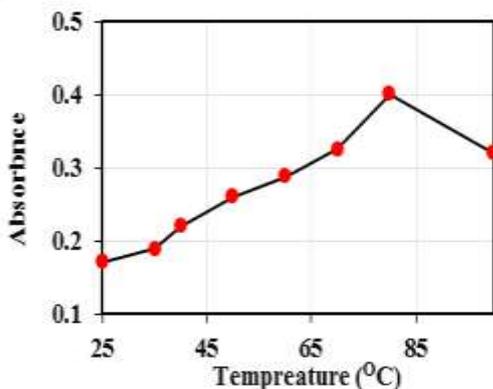


Figure (4): Effect of temperature on color reaction.

**Reaction time**

Optimum reaction time was determined by carrying out the coupling reaction at different periods (0-15 min). As shown in Figure (5), the absorbance value reaches to its maximum after 1 minute.

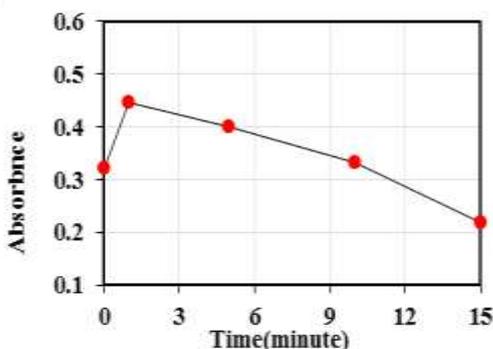


Figure (5): Effect of reaction time.

**Volume 5M NaOH**

The effect of different volumes (0.5-4.0 mL) of 5M sodium hydroxide solution on the reaction yield was investigated. The results show that 2.5 mL sodium hydroxide solution optimum and therefor recommended for the subsequent experiments, Figure (6).

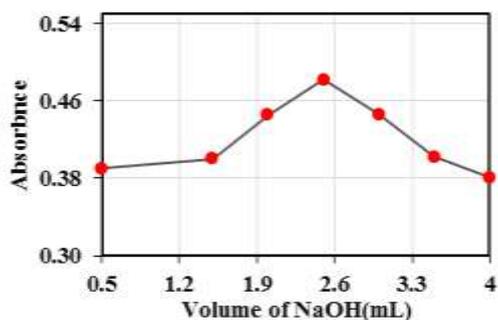


Figure (6): Effect of NaOH volume

**Final absorption spectrum**

The final spectrum of the azo dye product formed exhibits a maximum at 396 nm, under the optimum conditions shows in Figure (2).

**Nature of azo dye**

An azo dye is defined by having an azo linkage ( $--N=N--$ ) as part of its chromophore. Azo dyes are made in two steps:

1. A primary aromatic amine is reacted to give a diazonium salt.
2. The diazonium salt is reacted or coupled with a strongly activated aromatic system.

Job's method<sup>(13)</sup> and mole ratio method<sup>(14)</sup> have been used in the determination of the composition of the formed azo dye. The study shows that the ratio of CABZ to the diazotized sulfanilic acid in the formed azo dye was 1:1 for Job's and mole ratio methods. The results are depicted in Figures (7) and 8, and Scheme 1 shows the suggested structure.

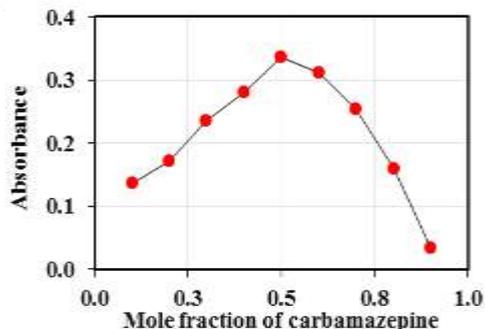


Figure (7): Job's method of continuous variation.

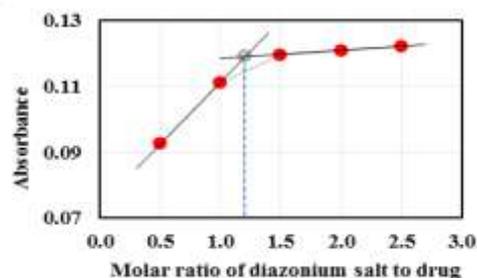
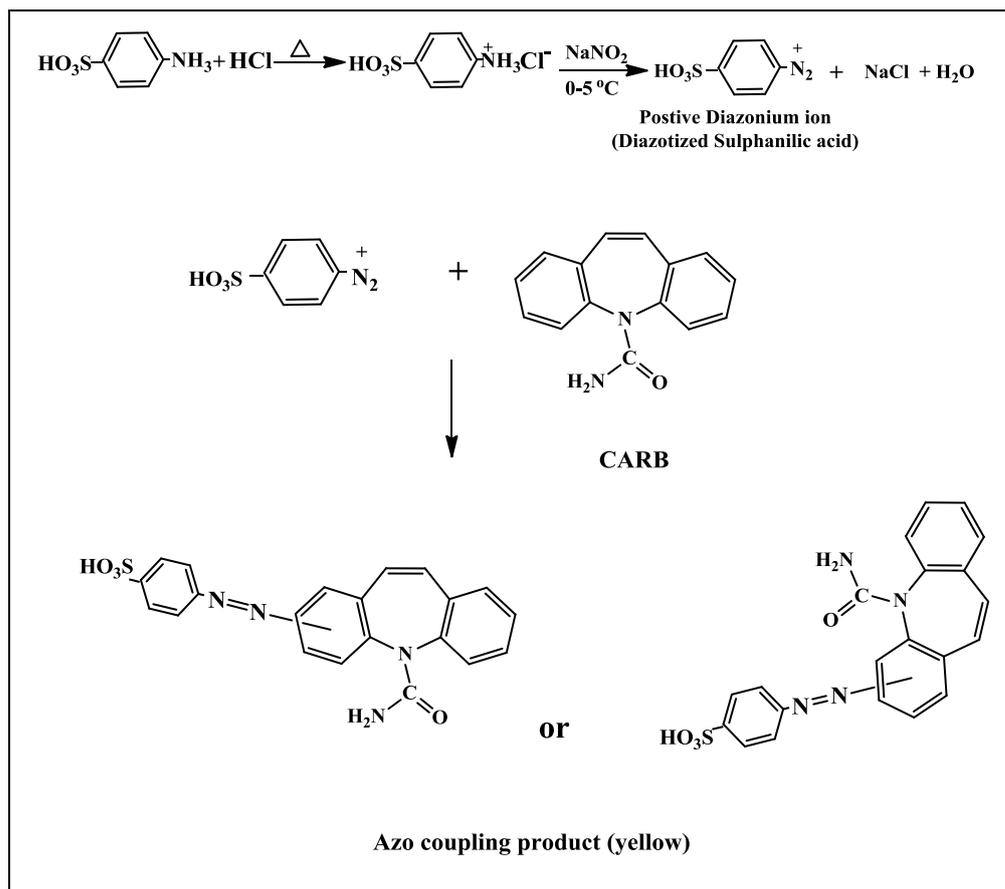


Figure (8): Mole ratio method



**Scheme (1): Steps of the main reactions between CARB and sulphanilic acid.**

### ***Kinetics of the reaction***

#### ***General procedure***

Aliquot of 0.6 mL of the standard drug solution containing various amount (6.0-36.0  $\mu\text{g}$ ) of CABZ was added to 0.8 mL of 0.01 M of the diazotized sulfanilic acid solution in a 25 mL conical flask. The mixture was shaken and left to stand for 1 minute at 80  $^\circ\text{C}$ , then after transferred into 4 mL cuvette. 1.6mL of 5M NaOH was then added and the absorbance of this solution was immediately measured at 396 nm. The value of absorbance was recorded at 1s intervals for 30 minutes (i.e. 0 and 1800s).

#### ***Verification of reaction order***

The rate of the reaction was studied to determine its order according to following equation<sup>(15,16)</sup>:

$$\text{Rate} = k'(\text{CABZ})^n$$

Where:  $k'$  and  $n$  represent the rate constant, and the order of the reaction.

This was accomplished by using different concentrations (2.0-18.0  $\mu\text{g}\cdot\text{mL}^{-1}$ ) of CABZ solution and a constant concentration ( $2.67 \times 10^{-3}$  M) of sulfanilic acid under the optimized conditions. It was found that the reaction rate is (CABZ) dependent. Graphs on Figure (9) shown

that reaction rate is increased with the increasing (CABZ) concentration.

Measurements carried out by variable time method, could be used for rate (in terms of  $\Delta A/\Delta t$ ) estimation.

The rate equation could also be expressed in logarithmic form as:

$$\log \text{rate} = \log \frac{\Delta A}{\Delta t} = \log k' + n \log(\text{CABZ})$$

Where:  $A$  is the absorbance, and  $t$  is the measuring time.

Regression least square plot of  $\log(\text{CABZ})$  versus  $\log(\text{rate})$  is shown in Figure (10). The regression equation is:

$\log(\text{rate}) = 1.1246 \log(\text{CABZ}) + 1.9528$ , with correlation coefficient ( $r$ ) = 0.9990. Accordingly, the value of  $k' = 89.702 \text{ s}^{-1}$  and the reaction is pseudo-first order since the value of  $n$  equals to 1.1246 ( $\approx 1$ ).

#### ***Quantitation methods***

The determination of CABZ was based on the above equation using the rate data. Different techniques were carried out (i.e. the initial rate, fixed concentration and fixed time) for this purpose. Appropriate method for analysis were selected according to their applicability, sensitivity, and the values of

correlation coefficient ( $r$ ) and intercept of the regression equations.

#### Rate constant method

The values of  $\log A$  vs time for different concentrations of CABZ were plotted. The plot was found to be linear in the range of  $8.4650 \times 10^{-6}$  -  $7.6190 \times 10^{-5}$  M. The values of  $k'$  (i.e. pseudo-first order rate constants) for the range of the studied concentrations were obtained by multiplying the values of slope by  $-2.303$  (Table 1).

**Table (1):  $k'$  values for various rates at different CABZ concentrations.**

| (Carbamazepine) M       | $k'$ ( $S^{-1}$ )      |
|-------------------------|------------------------|
| $8.4653 \times 10^{-6}$ | $-4.70 \times 10^{-5}$ |
| $4.2326 \times 10^{-5}$ | $-1.21 \times 10^{-4}$ |
| $6.3485 \times 10^{-5}$ | $-1.11 \times 10^{-4}$ |
| $7.6200 \times 10^{-5}$ | $-1.34 \times 10^{-4}$ |
| $7.6187 \times 10^{-5}$ | $-1.52 \times 10^{-4}$ |

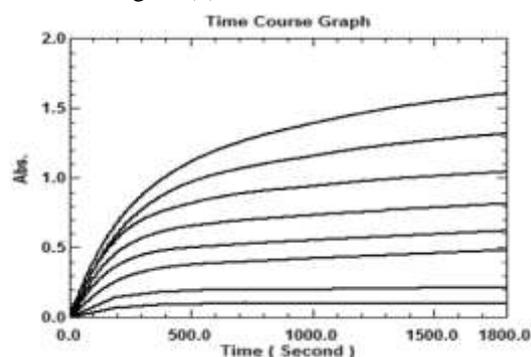
The regressed relation between  $C$  vs the values of  $k'$  is given by:

$$k' = -1.4837C - 4 \times 10^{-5} \quad (r = 0.9603)$$

The correlation coefficient value indicates poor linearity; thus, this method was abandoned.

#### Fixed absorbance method

The absorbance of CABZ reaction product for different concentrations of drug ( $1.6931 \times 10^{-5}$ –  $7.61873 \times 10^{-5}$  M) were recorded Figure (9).



**Figure (9): Absorbance-time curves for coupling of CABZ with diazonium salt; ( $C_{CABZ}$ ) = 2.0-18.0  $\mu\text{g.mL}^{-1}$ .**

The time in seconds at a selected value of absorbance (0.2294), was measured. A plot of the reciprocal value of measured time against initial (CABZ), (Table 2), was constructed with the following regression equation:

$$\frac{1}{t} = 289.96 C - 0.0008 \quad (r = 0.9694)$$

The value of correlation coefficient ( $r = 0.9694$ ) for calibration graph indicated poor,

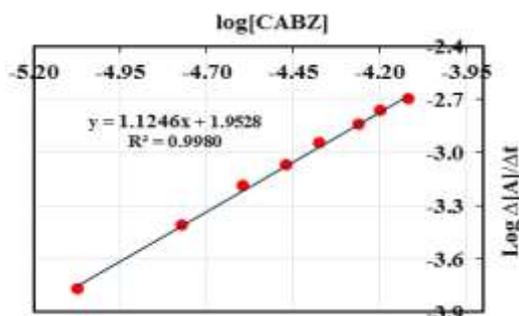
which is considered a disadvantage. Table 2 summarize the values of  $(1/t)$  for different CABZ concentration.

**Table (2): Reciprocal time values for fixed absorbance at different (CABZ).**

| (CARB) M x $10^{-5}$ | $1/t$ ( $S^{-1}$ ) x $10^{-3}$ |
|----------------------|--------------------------------|
| 1.6931               | 1.793                          |
| 2.5396               | 6.461                          |
| 3.3861               | 10.712                         |
| 4.2326               | 13.131                         |
| 5.5024               | 16.169                         |
| 6.3489               | 16.282                         |
| 7.6187               | 20.353                         |

#### Initial rate method

In this method, the reaction in the initial rate with respect the time in the (0-600 sec.) versus the  $\log$  (CABZ) plots were rectilinear within the range of 2.0 – 18.0  $\mu\text{g.mL}^{-1}$  Figure (10). The reaction was first order by according to the value of slope 1.1246 ( $\approx 1$ ) and the value of correlation coefficient was (0.9990).



**Figure (10): Calibration plot of logarithm rate of the reaction against logarithm molar concentration of CABZ for initial rate method.**

The value of detection limit was calculated and found to be  $0.0730 \mu\text{g.mL}^{-1}$  while limit quantification was  $0.2434 \mu\text{g.mL}^{-1}$ . These values indicated the high sensitivity of the proposed method to determine low amounts of CABZ.

#### Fixed time method

In the fixed time method, varying amounts of CABZ were used for determination of reaction rate at a preselected fixed time (1, 5, 10, 15, 20, 25 and 30 minute) and the absorbance values were measured and plotted against (CABZ).

The low values of standard deviation (SD), limit of detection (LOD) and limit of quantification (LOQ) are given in (Table 3). A fixed time of 10 minute indicates that this method could successfully applied for determination of CABZ in its pure form and in pharmaceutical preparations. Figure (11).

Table (3): Regression equations at fixed time method for the determination of CABZ.

| Time (min) | Regression equation | Correlation coefficient (r) | *SD <sub>Δy</sub> | **LOD (μg.mL <sup>-1</sup> ) | ***LOQ (μg.mL <sup>-1</sup> ) |
|------------|---------------------|-----------------------------|-------------------|------------------------------|-------------------------------|
| 1          | Y= 0.0152C + 0.0077 | 0.9812                      | 0.0166            | 3.2829                       | 10.9431                       |
| 5          | Y= 0.0511C + 0.0137 | 0.9934                      | 0.0327            | 1.9227                       | 6.4091                        |
| 10         | Y= 0.0693C - 0.0353 | 0.9993                      | 0.0137            | 0.5950                       | 1.9834                        |
| 15         | Y= 0.0784C - 0.0666 | 0.9993                      | 0.0159            | 0.6080                       | 2.0267                        |
| 20         | Y= 0.0848C - 0.0854 | 0.9987                      | 0.0235            | 0.8328                       | 2.7760                        |
| 25         | Y= 0.0894C - 0.0947 | 0.9982                      | 0.0293            | 0.9838                       | 3.2793                        |
| 30         | Y= 0.0927C - 0.0961 | 0.9978                      | 0.0338            | 1.0923                       | 3.6412                        |

\*SD = for the difference absorbance, \*\*LOD = 3.3 σ/S and \*\*\*LOQ = 10 σ/S.

Table (4): Validation of regression and assay for the determination of CABZ by the proposed method.

| Parameter   | Fixed time method (10 mint.) | Initial rate method |
|---|------------------------------|---------------------|
| λ <sub>max</sub> (nm)                                       | 396.0                        |                     |
| Regression equation   | Y=0.0693C-0.0353             | Y=1.1246C+1.9528    |
| Linearity (μg mL <sup>-1</sup> )                            | 2.0-18.0                     |                     |
| Slope ± SD  | 0.0693±0.00101               | 1.1246±0.0207       |
| Intercept ± SD  | 0.0353± 0.0109               | 1.9528±0.0928       |
| Correlation of linearity (R <sup>2</sup> )                  | 0.9987                       | 0.9980              |
| Correlation coefficient (r)                                 | 0.9993                       | 0.9990              |
| Molar absorptivity (L.mol <sup>-1</sup> .cm <sup>-1</sup> ) | ε =16373.4140                | ε =265707.6         |
| Sandell's sensitivity(μg.cm <sup>-2</sup> )                 | 0.01433                      | 0.00089             |
| Limit of detection (μg.mL <sup>-1</sup> )                   | 0.5950                       | 0.0730              |
| Limit of quantification (μg.mL <sup>-1</sup> )              | 1.9834                       | 0.2434              |
| t-test*   | 4.4653                       |                     |

\*Theoretical value for t-test for N=2, at 95% confidence limit is 4.303

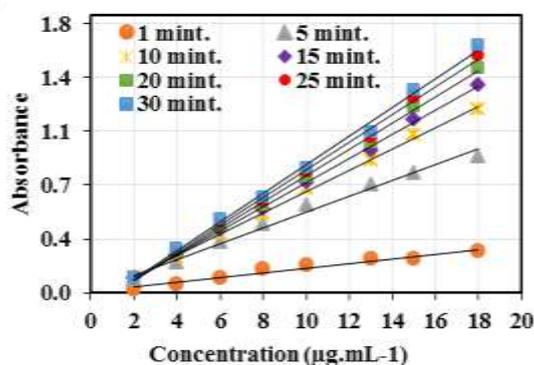


Figure (11): Calibration plot of absorbance versus the concentration of CABZ at preselected fixed time.

#### Validation of the proposed methods

##### Accuracy and precision

Intraday relative standard deviation percent and relative error percent of the results obtained by the recommended methods (initial rate and fixed time) were calculated for three replicates within the day using pure drug solutions at two CABZ concentration levels (3.0 and 6.0 μg.mL<sup>-1</sup>) within the working ranges. The value of RSD % did not exceed 2% while percent relative error (RE %), an indicator of accuracy, was ≤ 5.5475. This good level of relative error for each proposed methods could be consider as adequate for the quality control analysis of the studied CABZ. The analytical results obtained from the investigation are summarized in (Table 5).

**Table (5): Accuracy and precision of the initial rate and fixed time methods for determination of CABZ.**

| Method       | Conc. of carbamazepine ( $\mu\text{g.mL}^{-1}$ ) |        | RE%     | RSD%   |
|--------------|--|--------|---------|--------|
|              | Taken  | Found* |         |        |
| Initial rate | 3.00   | 3.1598 | 5.3256  | 0.5768 |
|              | 6.00   | 6.0213 | 0.3546  | 1.8157 |
| Fixed time   | 3.00   | 3.1664 | 5.5475  | 0.7153 |
|              | 6.00   | 5.8076 | -3.2067 | 1.8617 |

\*Average of three measurements.

#### Application of the proposed methods

The results obtained for the two suggested kinetic spectrophotometric methods to analyses CABZ were satisfactory due to their good agreement with the labeled amounts.

The results shown in Table (6) are for the analysis of CABZ in commercial tablet by

both methods (initial rate and fixed time). The mean recoveries and RSD% values were  $101.7245 \pm 1.4561\%$  and  $101.0922 \pm 1.4861\%$  respectively.

**Table (6): Analysis of CABZ by the initial rate and fixed time methods.**

| Sample                              | Method       | Conc. of CABZ ( $\mu\text{g.mL}^{-1}$ ) |         | *Recovery % | *S. D. | *RSD%  |
|-------------------------------------|--------------|---|---------|-------------|--------|--------|
|                                     |              | Taken                                   | *Found  |             |        |        |
| Taver (Cyprus) 200mg/tablet         | Initial rate | 2.00                                    | 2.0411  | 102.0545    | 0.0354 | 1.7357 |
|                                     |              | 7.00                                    | 7.0353  | 100.5045    | 0.1101 | 1.5643 |
| Tegral (Egypt) 200mg/tablet         |              | 10.00                                   | 10.0279 | 100.2791    | 0.1187 | 1.1832 |
|                                     |              | 15.00                                   | 14.9465 | 99.6431     | 0.3050 | 2.0406 |
| Tegratol (Switzerland) 200mg/tablet |              | 6.00                                    | 6.4273  | 107.1223    | 0.0710 | 1.1052 |
|                                     |              | 12.00                                   | 12.0893 | 100.7437    | 0.1339 | 1.1075 |
| Taver (Cyprus) 200mg/tablet         | Fixed time   | 2.00                                    | 2.0789  | 103.9442    | 0.0306 | 1.4730 |
|                                     |              | 7.00                                    | 6.8211  | 97.4483     | 0.1110 | 1.6270 |
| Tegral (Egypt) 200mg/tablet         |              | 10.00                                   | 9.9120  | 99.1202     | 0.1251 | 1.2624 |
|                                     |              | 15.00                                   | 15.2386 | 101.5907    | 0.3382 | 2.2196 |
| Tegratol (Switzerland) 200mg/tablet |              | 6.00                                    | 6.2110  | 103.5170    | 0.0709 | 1.1412 |
|                                     |              | 12.00                                   | 12.1120 | 100.9329    | 0.1445 | 1.1931 |

\*Average of three measurements.

## Conclusion

In present study, determination of CABZ in its pure form and in its pharmaceutical dosage was investigated by two new kinetic methods (initial rate and fixed time). It was found that the proposed methods are precise, accurate, and sufficiently sensitive to be applied for determination of small amounts of CABZ. Therefore, the proposed methods could be recommended for the analysis of CABZ in quality control laboratories.

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