Uni and Multivariate Optimization for the Spectrophotometric Determination of Cimetidine Drug via Charge-Transfer Complex Formation

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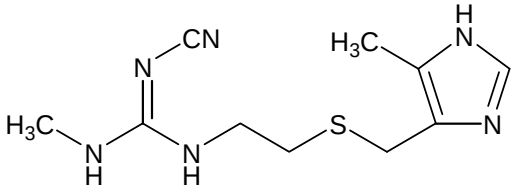
Abstract

Charge transfer complex formation method has been applied for the spectrophotometric determination of cimetidine, in bulk sample and dosage form. The method was accurate, simple, rapid, inexpensive and sensitive depending on the formed charge- transfer complex between cited drug and, 2,3-Dichloro-5,6-dicyano-p- benzoquinone (DDQ) as a chromogenic reagent. The formed complex shows absorbance maxima at 587 nm against reagent blank. The calibration graph is linear in the ranges of (5.0 - 50.0) $\mu g.mL^{-1}$ with detection limit of $0.268 \mu g.mL^{-1}$. The results show the absence of interferences from the excipients on the determination of the drug. Therefore the proposed method has been successfully applied for the determination of cimetidine in pharmaceutical preparations.

Keywords: Simplex, Spectrophotometric, Cimetidine , Charge- transfer.

Introduction

Cimetidine, or N-Cyano-N-methyl-N-[2-[5-[[methylimidazol-4-yl] thio]ethyl] guanidine [1], is an H_2-receptor antagonist drug which reduces the volume and hydrogen ion concentration of gastric juice, it is used for the treatment of duodenal ulcers, Zollinger-Ellison syndrome, and other gastric hypersecretory states [2]. It's also indicated for the relief heartburn and prevents rebleeding in patients of peptic and duodenal ulcers [2,3]. Cimetidine, due to its effects on the immune system and as an H_2-receptor antagonist, can inhibit growth of carcinogen-induced colonic tumors in rats, as well as the in vitro human colon cancer cell lines[4]. The Chemical structure of cimetidine is given in (Scheme 1).



Scheme (1)

Several methods have been reported for determination of cimetidine in bulk and pharmaceutical dosage forms, these methods include titrimetry [5], high performance thin layer chromatography [6], high performance liquid chromatography[7-9], liquid-liquid extraction[10] and Potentiometry [11,12].

Spectrophotometry [13-18] are most convenient techniques because of their inherent simplicity, adequate sensitivity, low cost and wide availability in all quality control laboratories.

In experimental chemistry, the optimization of technical system is the process of the adjusting of the control variables to find the levels that achieve the best optimization. Usually, many conflicting response must be optimized simultaneously. In lack of systematic approaches the optimization is done by trial and error, or by changing one control variable at a time while holding the rest constant, such methods requires a lot of experiments to be carried out.

Simplex optimization of experimental parameters was first introduced by Spendley [19], and then modified by Nelder [20] and Aberg [21].

Simplex is a geometric figure in which there are n +1 vertices, where (n) represents the number of variables [22], the method found a lot of applications in field of analytical chemistry [23-25], because it offers the capability of optimizing several factors simultaneously depending on a statistical design search to find out the maxima or minima of response, by rejecting the point producing the worst response and a replacement of it by the new point which is obtained statistically.

The present work describes the utility of 2,3-Dichloro-5,6-dicyano-p-benzoquinone (DDQ) reagent for spectrophotometric determination of cimetidine in pure form as well as in these dosage forms. In addition, the optimization of chemical dependent variables of affecting absorbance have been studied by using modified simplex method via computer program.

Apparatus

A cintra 5 spectrophotometer with 1 cm quartz cells were used for absorbance measurements. PH-meter DW-9421 from Philips instrument, a Sartorius BL 210S balance, and a Pentium 4 computer (DELL) was used for data processing.

Experimental

Material and Reagents

All chemicals used were of analytical reagent grad unless otherwise is mentioned, cimetidine standard powders (purity 99.8%) were kindly provided by the State Company for Drug Industries and Medical Appliances, Samara-Iraq (SDI).

DDQ 0.1 %(w/v) solution, was prepared by dissolving 0.01 g of the DDQ in 5 mL of acetonitrile and then the solution was diluted to a final volume 10 mL with acetonitrile. Working solutions were freshly prepared by subsequent dilutions. This solution is prepared daily using red- glass volumetric flask because it is a light sensitive reagent.

Standard Drugs Solutions

Cimetidine stock solution (500 $\mu g.mL^{-1}$), was prepared by dissolving 50 mg of Cimetidine in 5mL methanol and diluting to 100mL in a volumetric flask with acetonitrile. Working solutions were freshly prepared by subsequent dilutions.

General Recommended Procedure

Measured volumes of the standard stock solution of the drug containing (25-250 µg) were transferred into 5-mL calibrated flasks, 0.3 ml of 0.1% DDQ solution was added to each, and then diluted to volume with acetonitrile. Absorbance measurements of resulting solutions were done at the wavelength of maximum absorption (587nm) against reagent blank which prepared by the same manner, but without addition of cimetidine.

Analysis of Cimetidine in Pharmaceutical Preparations

The content of 10 tablets were mixed well and a certain amount of fine powder was accurately weighted to give an equivalent to 200 mg for tablets and dissolve in 50 mL of methanol, swirled, left to stand for 5 mints and diluted to 100mL in a volumetric flask with acetonitrile. The solution then was filtered by using Whatman filter paper No.41 to avoid any suspended or undisclosed material before use, and the first portion of the filtrate was rejected, Working solutions were freshly prepared by subsequent dilutions with acetonitrile and analyzed by the recommended procedure.

Results and Discussion

Spectrophtometric procedures are popular for their sensitivity in the assay of drugs and hence, charge-transfer complex formation has received considerable attention for the quantitative determination of many pharmaceutical compounds [26-28].

Cimetidine react with DDQ to give yellow color charge-transfer complex, which exhibits absorption maxima at 587 against their reagent blank (Figure1). The some bands may be attributed to the formation of DDQ radical anion, which probably resulted from the dissociation of the donor-acceptor complex in relatively high polar solvents like acetonitrile

[28]. Therefore, in order to avoid the maximum interference from the reagent blank, the absorbance measurements were carried out at 587 nm in the subsequent work.

Optimization of experimental variables

I. Univariable Method

The experimental variables affecting the development and stabilities of charge-transfer complex formation were achieved through a number of preliminary experiments. Such factors include reagent volume, reaction time, temperature, and the type of organic solvent. For this reason, a variable was modified while maintaining the other variables at their constant values, then by maintaining that variable at its optimized value, another was modified; all variables were optimized via this method.

Effect of Reagent Volume:

The influence of amount of the used reagent on the absorbance of cimetidine–DDQ complex is illustrated in (Figure 2). 0.3mL of 0.1% solution of DDQ was found to be optimum to develop the maximum color intensity for formed charge-transfer complex, after which no more increase in absorbance values was obtained; therefore, the cited amount of DDQ solution was used.

Effect of reaction time

The optimum reaction time is determined by following the color development at ambient temperature (25 ± 2 °C). It was found that the reaction of cimetidine with DDQ, under the conditions of the study, is instantaneous, and the formed complex attained maximum absorbance immediately after mixing. The developed color remained strictly unaltered for at least 2 hours in dark place.

Effect of Temperature

The optimum reaction temperature was determined by following the color development at ambient temperature in the range from (25 - 50 ± 2°C). It was found that the reaction between cimetidine and DDQ is independent on the temperature of the medium up to 40 °C; hence the absorbance of the complex remains, approximately, constant. The value of the absorbance starts to decrease considerably when reaction temperature raised above 40 °C, this may be due to decomposition of the formed charge transfer complex. 25°C was chosen to be optimum, because the product attained maximum and constant absorbance (Figure 3).

Effect of Organic Solvent

Several organic solvents, namely acetonitrile, dichloromethane, chloroform, methanol, benzene, 1,2-dichloroethane, in addition to water, were examined for their ability to solvate the reaction constituents and to results in maximum absorbance for cimetidine – DDQ charge transfer complex. Acetonitrile was found to be the most suitable solvent to achieve quantitative recovery of cimetidine complex (Table 1).

II. Simplex Method

Simplex method used to optimize the required reagent volume, reaction time and the reaction temperature. After choosing the convenient boundary conditions for each of the mentioned

control variables, four arbitrary experimental conditions should were carried out (Table 2) and the results were entered to the Multi-simplex program points (1 to 4) in Table 3.
The Simplex program starts to reflect the worst point through the centroid of other points to obtain a new point 5. An experiment was then performed utilizing the variable setting as a reflected point; because this value was better than that at point 1, the latter was rejected and replaced by point 5. A measured absorption signal was feeding again to the program and the process is repeated successively until the optimum conditions are obtained and were similar to those obtained by the univariate method.

Calibration Graph

Employing the optimum experimental conditions, a linear calibration graph for the determination of cimetidine, by charge-transfer complex formation with DDQ, was obtained (Figure 4), which shows that Beer's law was obey in the concentration range of (5.0-50.0) $\mu g.mL^{-1}$, with a correlation coefficient (R= 0.9997) and detection limit of 0.268 $\mu g.mL^{-1}$.

Spectral Characteristics of the Proposed Method

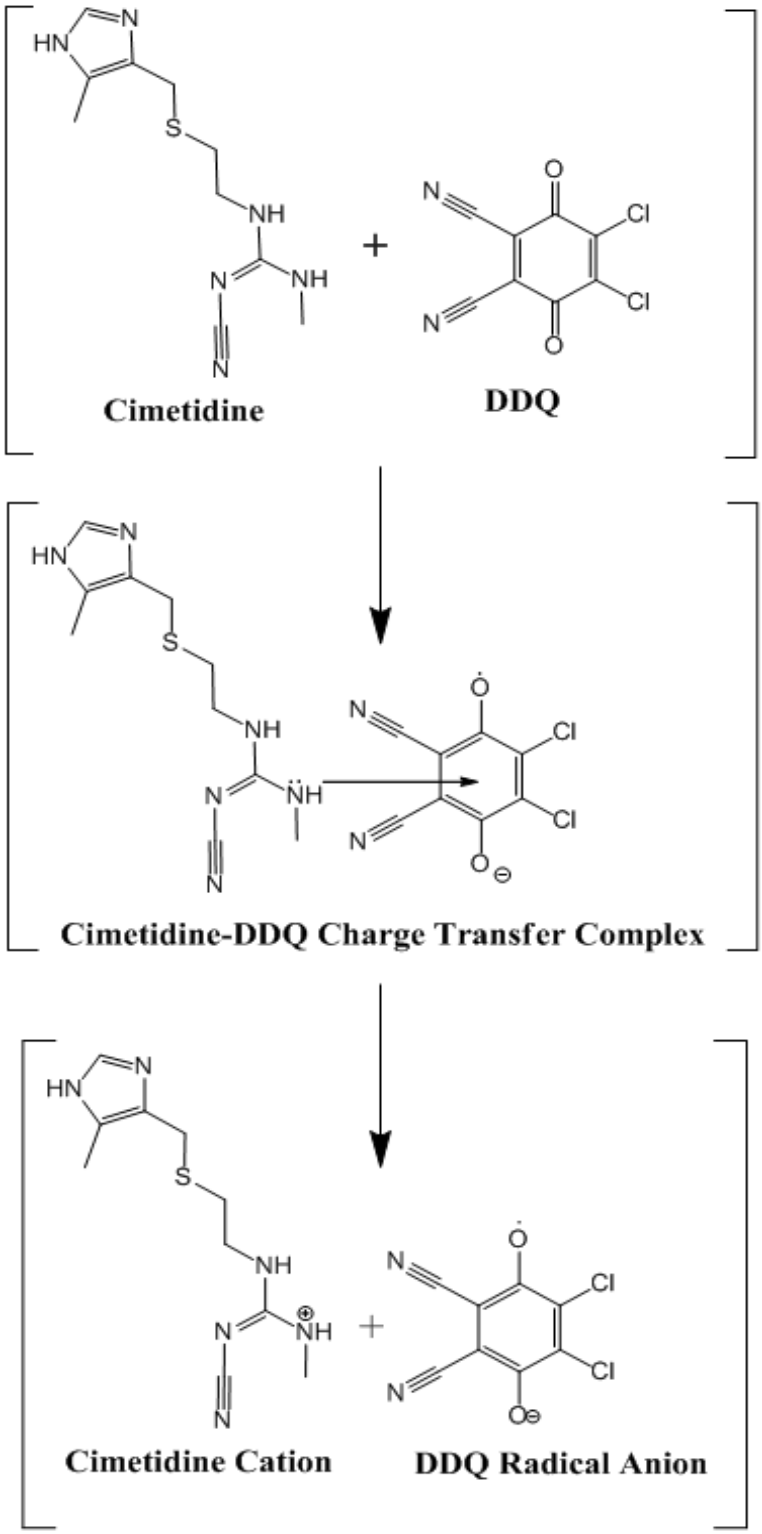
Under optimum experimental conditions of the proposed method, the regression plot showed linear dependence of absorbance signals on the concentrations of the studied drug in the range given. The regression equations, correlation coefficients, molar absorptivities, detection limits and sandell sensitivity in addition to other parameters are given in Table 4.

Stoichiometry of the Complex

To propose a structure for the formed charge transfer complex between cimetidine and DDQ, two analytical procedures (Slope analysis and Job's of continuous variation method) were followed, Figures 5, 6 and 7 respectively. The results, in both studies, showed that the complex is composed from DDQ and cimetidine with a ratio of 1:1 (DDQ: cimetidine).

$$\text{Ratio} = \text{Slope R} / \text{Slope D} = 4795 / 4793 = 1.00042 \simeq 1$$

The structure of the formed charge transfer complex can be represented as in Scheme 2. The mechanism of the reaction depends on the formation of an original donor-acceptor (DA) complex through the interaction between one of the nitrogen atoms of amine moieties in the cimetidine (as n-electron donor) and DDQ (as π-acceptor). Then, the dissociation of DA-complex may be promoted by the solvent, especially that with high ionizing power such as acetonitrile, where complete electron transfer from the donor to the acceptor moiety takes place. This is followed by formation of the DDQ radical anions as a predominant chromogen [29].



Scheme (2)

Accuracy and Precision

The accuracy and precision of the proposed method was checked by analyzing three replicates of three different concentration levels of the drug (within Beer's law range). The accuracy was determined by calculating the relative error percentage, while the precision was tested by calculating the percentage relative standard deviation (%RSD). The results indicated good accuracy with resonable precision of the proposed method (Table 5).

The proposed method was advantageous when compared statistically with other methods found in the literature in having good sensitivity and the results are shown in Table 6.

Interferences Study

The results showed that no interferences were found in the presence of up to 500 $\mu g.mL^{-1}$ of the studied excipients (lactose, sucrose, starch, glucose, magnesium stearate and sodium citrate) in the determination of cimetidine (Table 7).

Analysis of Dosage Forms

The applicability of the proposed method for the determination of cimetidine in commercial dosage form was examined by analyzing of their content of the active ingredient by the proposed method (charge-transfer complex formation). The results given in Table 8, reveal that the recoveries were in the range of, reflecting high accuracy and precision of the proposed method as indicated by low percentage relative standard deviation value. The recommended method was statistically compared with official, standard and other methods, no significant differences were found between the calculated and theoretical values of t and F-test at 95% confidence limit (Table 9).

Conclusions

The utility of DDQ reagent for the spectrophotometric determination of cimetidine was established. The method based charge-transfer complex formation between the cited drug and DDQ as a chromogenic reagent. The proposed method was found to be accurate, simple and sensitive. It was satisfactorily applied to the determination of cimetidine in pharmaceutical product samples.

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Table (1): Effect of different solvents on the determination of 20µg.mL^{-1}cimetidine; 0.1% DDQ.

Solvent	Absorbance
Acetonitrile	0.432
Dichloromethane	0.259
Chloroform	0.158
Methanol	0.128
Benzene	0.057
1,2-Dichloroethane	0.119
Water	0.028

Table (2): Boundary of Simplex indeprndent variables for determination of cimetidine.

Variable	Range	Step size
Reagent volume (mL)	0.1-0.5	0.1
Reaction Time (min.)	0-20	5.0
Temperature (°C)	25-45	5.0

Table (3): Multivariate experiments (Simplex) for the determination of 20 µg.mL^{-1} cimetidine.

Exp. No.	Reagent volume (mL)	Reaction time (min.)	Temperature (°C)	Abs.	Operation
1	0.1	0	25	0.256	
2	0.4	20	25	0.328	
3	0.2	20	45	0.322	
4	0.5	10	35	0.354	
5	0.5	20	45	0.317	R
6	0.3	5	30	0.427	C
7	0.5	0	25	0.404	R
8	0.4	0	35	0.408	R
10	0.2	0	25	0.410	R
11	0.1	5	35	0.233	R
12	0.4	0	25	0.416	R
13	0.2	5	25	0.392	C
14	0.4	0	30	0.411	R
15(13)	0.2	5	25	0.392	R
16	0.5	5	35	0.382	C
17	0.3	0	25	0.432	C
18	0.3	0	30	0.430	C
19(10)	0.2	0	25	0.410	C

Table (4): Spectral characteristics and statistical data of the regression equation for determination of cimetidine via charge transfer formation.

Parameter	Value
λ_{max} (nm)	587
Color	yellow
Linearity range ($\mu g.mL^{-1}$)	5.0-70.0
Molar absorptivity ($L.mol^{-1}.cm^{-1}$)	4794.441
Regression equation	A = 0.0190 [Cim. $\mu g.mL^{-1}$] + 0.0564
Calibration Sensitivity	0.0190
Sandell's Sensitivity ($\mu g.cm^{-2}$)	52.632
Correlation of Linearity (R^2)	0.9994
Correlation coefficient (R)	0.9997
Detection limit ($\mu g.mL^{-1}$)	0.268

Table (5): Evaluation of accuracy and precision for the determination of cimetidine by proposed procedure.

Conc. ($\mu g.mL^{-1}$)		Relative Error %	R.S.D.* %
Taken	Found*		
10	9.920	-0.800	2.016
20	19.69	-1.550	2.792
40	39.436	-1.410	1.805

Average of three determinations*

Table (6): Analytical parameters for the analysis of cimetidine by the proposed and others methods.

Ref. No.	methods	Linear range $\mu g.mL^{-1}$	ε $L.mo^{-1}.cm^{-1}$	Correlation Coefficient (R)	Recovery	RSD%
18	Spectrophotometric	8.0-30.0	6710		99.8-100.2	0.810-0.840
5	H.P.TL.C.	5-50	-	-	100.39 ± 1.33	
6	H.P.L.C	0.25-83.0		0.998	99.2 - 100.8	
17	Spectrophotometric 1st derivative	25.0-150.0	-	-	100.27±0.679	-
	Spectrophotometric Complex formation	10.0-60.0	-	-	99.84±0.858	-
-	Proposed method	5.0-70.0	4794.441	0.9997	98.485-99.200	1.805-2.792

Table (7): Percent recovery for 20 µg.mL^{-1}of cimetidine in the presence of 500 µg.mL^{-1}of excipients.

Excipients	Cimetidine Conc. Taken (20 µg.mL^{-1})	
	Conc. Found (µg.mL^{-1})	%Recovery
Lactose	20.155	100.775
Sucrose	20.199	100.995
Starch	19.845	99.225
Glucose	19,888	99.440
Magnesium Stearate	19.929	99.645
Sodium Citrate	19.869	99.345

*Average of three determinations.

Table (8): Spectrophotometric determination of cimetidine in pharmaceutical preparations via charge-transferee complex formation with DDQ.

Sample	Labeled amount (mg)	Found amount (mg)	Conc. taken (µg.mL^{-1})	Conc. Found* (µg.mL^{-1})	Relative Error %	Rec. %	R.S.D* %
CIMETIDINE (Cimetidine) 200 mg Tablet UK	200	202.26	10	10.113	1.130	101.13	1.331
		202.04	20	20.204	1.020	101.02	2.214
Tagadine (Cimetidine) 200mg/ tablet SDI Iraq	200	203.46	10	10.173	1.730	101.73	2.860
		202.25	20	20.225	1.125	101.13	1.510
Cimedne^{R} (Cimetidine) 200mg/ tablet DAD Jordaan	200	186.84	10	9.342	-6.580	93.420	2.419
		186.83	20	18.683	-6.585	93.415	1.584

*Average of three determinations.

Table (9): t- and F-values for analysis of cimetidine in pharmaceutical compounds for proposed (S.D.I.), and others methods.

Proposed Method	T-Values[a]	F-values[b]	Other Methods(N=5)	μ	S.D	Ref. No.
N=3 S.D = 0.286 μ = 10.173 T^c =1.048	0.706	5.000	Official	9.890	0.640	18
	0.393	10.550	Other	9.950	0.930	30
	0.979	14.643	Stander	10.020	0.167	31

a- Theoretical values for T-test at 95% confidence limit were N=6 (2.447).

b- Theoretical values for F-test at 95% (19.247) confidence limit, were N=(4,2), (4,2) and 99% (18.000) were N=(2,4) respectively,

c- Theoretical values for T at 95% confidence limit were N=2(4.303).

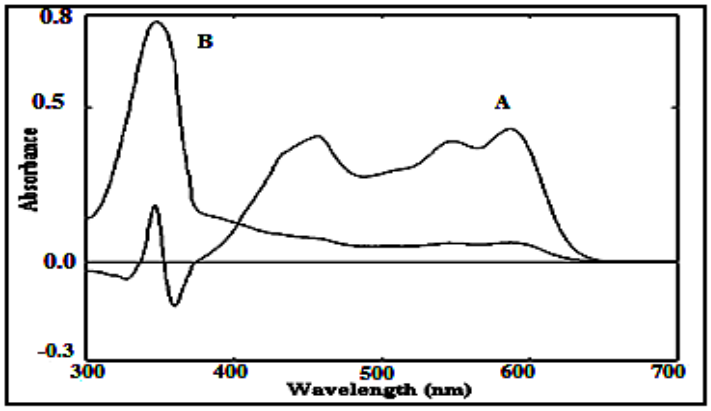

Fig. (1): Absorption spectra (A) of 20μg.mL^{-1} cimetidine-DDQ charge-transfer complex, (B) of the blank solution under the recommended procedure

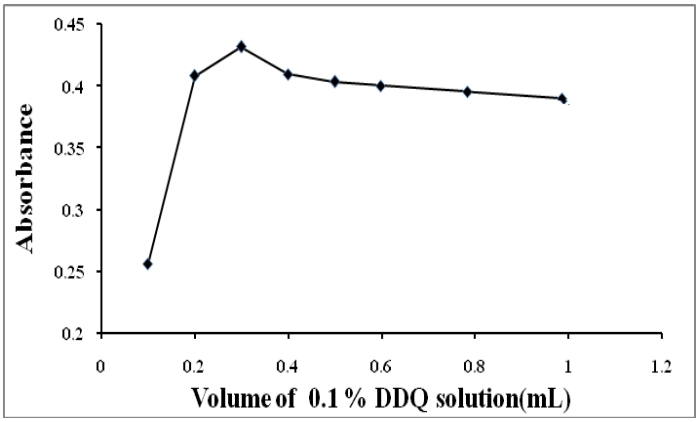

Fig. (2): Effect of reaction time on the absorbance of 20 μg.mL^{-1} cimetidine; 0.1% DDQ.

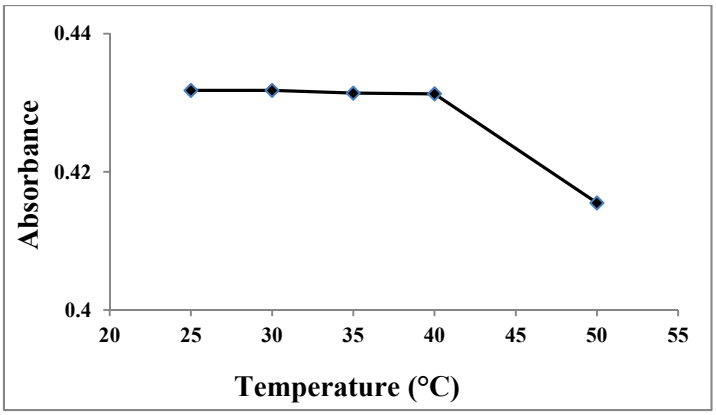

Fig. (3): Effect of temperature on the absorbance of 20 µg.mL^{-1} cimetidine; 0.1% DDQ.

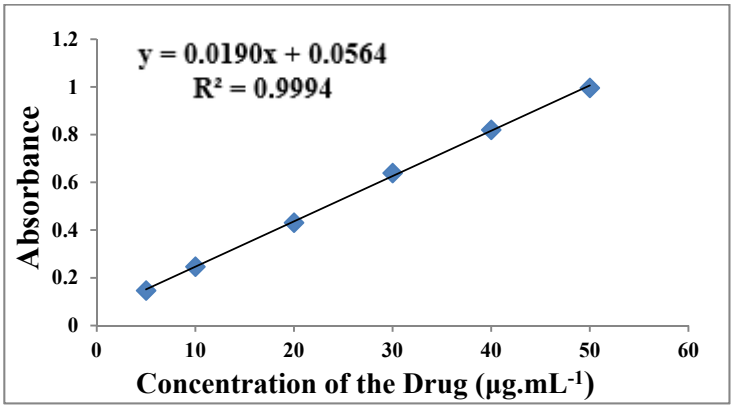

Fig. (4): Calibration graph of cimetidine under optimum experimental conditions.

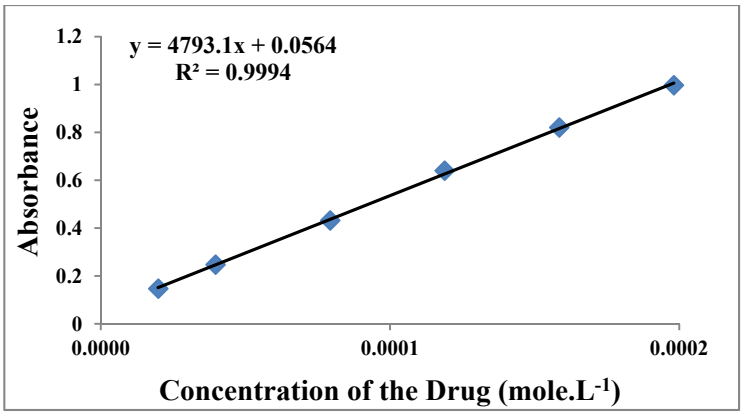

Fig. (5): Results obtained for the slop ratio method, with variable concentrations of cimetidine; (2.643x10^{-4}M DDQ).

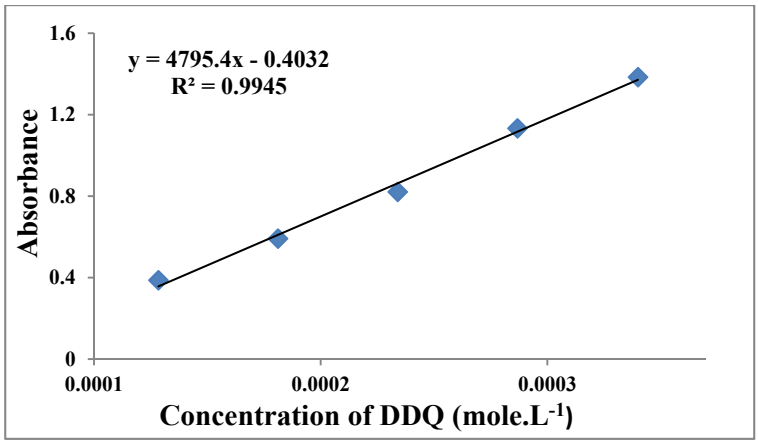

Fig. (6): Results obtained for the slop ratio method, with variable concentrations of DDQ; (1.590x10^{-4}M) cimetidine.

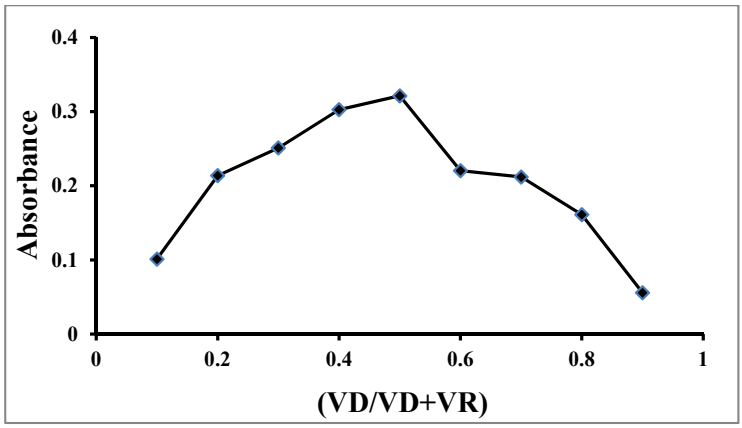

Fig. (7): Continuous variation of 9.907 x10^{-4} M cimetidine, 9.907 x10^{-4} M DDQ.

ايجاد الظروف الفضلى بدراسة المتغيرات الاحادية والمتعددة لتقدير دواء السميتيدين بتكوين معقد الازدواج الايوني

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استلم البحث في:7/أيار/2015، قبل البحث في:14/حزيران/2015

الخلاصة

تم استعمال طريقة طيفية لتقدير السميتيدين في عينات نقية وفي المستحضرات الصيدلانية. كانت الطريقة دقيقة، بسيطة، سريعة، غير مكلفة وحساسة تعتمد بالاساس على تكوين معقد انتقال الشحنة بين العقار قيد الدراسة مع الكاشف2،3 ثنائي كلورو 5،6 بارا بنزوكيونون(DDQ) ككاشف لوني. اظهر المعقد المتكون اعظم امتصاص له عند الطول الموجي 587 نانومتراً مقابل محلول الخلب، فقد اظهر منحني المعايرة علاقة خطية ضمن المدى من التراكيز (5.0 – 50) مايكروغرام / مل وبحد كشف 0.268 مايكروغرام/ مل. أظهرت الدراسة أيضاً أن الطريقة المقترحة خالية من تأثير المتداخلات المتعارف على وجودها في المستحضرات الصيدلانية، فقد أمكن تطبيق الطريقة بنجاح لتقدير السميتيدين في بعض تلك المستحضرات.

الكلمات المفتاحية: سمبلكس، طيفيي، سميتيدين، انتقال الشحنة.