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RESEARCH ARTICLE

Spectrophotometric determination of Risperidone in pharmaceutical preparations by Charge-Transfer Reactions

***M. E. M. Hassouna[1] and G. A. Zaki**

Chemistry Department, Faculty of Science, Beni-Suef University, Beni-Suef, Egypt

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****Corresponding Author***

M. E. M. Hassouna

Abstract

A simple, rapid and sensitive method for the spectrophotometric determination of risperidone (RIS) has been developed. The proposed method is based on the charge–transfer reactions of risperidone as electron donor, with 7,7,8,8,-tetra-cyanoquinodimethane (TCNQ) , 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) , tetracyanoethylene (TCNE) and chloranilic acid(CA) as π-acceptors to give colored complexes. The experimental conditions such as reagent concentration, reaction solvent, temperature and time have been optimized to achieve the highest sensitivity. Beer's law is obeyed over the concentration ranges of 8 – 150, 25 – 250, 5 – 70 and 10 – 110 μgml^{-1} risperidone using DDQ, CA, TCNE and TCNQ respectively, with corresponding correlation coefficients of 0.9995, 0.9993, 0.9990 & 0.9997 and detection limits of 3.62, 8.66, 1.93 and 2 .85 μgml^{-1} for the reagents in the same order

1. INTRODUCTION

The properties of charge-transfer (CT) complexes formed in the reaction of electron acceptors with donors containing nitrogen, sulfur, oxygen atoms[1],as well as amines polysulfur and crown ethers bases have attracted considerable attention and growing importance in recent years[2-12]. This is owing to the important role of charge transfer which is played in biological systems as well as to the significant physical properties of the CT-products such as electrical conductivities[13&14] and their applications in many forms of electronic and solar cells[15&16] and in the analysis of some drugs and pharmaceutical preparations[17-20]. The important role is also played by the charge transfer complexes in the quantitative estimations of drugs[21&22]. Charge-transfer complexation is of great importance in chemical reactions including addition, substitution, condensation[23]. The protonation of the donor from acceptors are generally root for the formation of ionpair adducts[24].The chemical and physical properties of CT complexes formed in the reactions of π- and σ-electron acceptors with different donors like amines, polysulfur, crown ethers bases and oxygen–nitrogen mixed bases have been the subjects of many investigations both in solution and in solid state. Some researchers have studied the CT interactions between the drugs and various acceptors to throw light on the role of weak interactions in understanding drug–receptor mechanism.

Riperidone (RIS), 3 – [2 – [4 –(6 – Fluoro – 1,2 – benzisoxozol – 3 –yl] ethyl] -2 – methyl – 6, 7,8, 9 – tetrahydro – 4 H – pyrido [1,2 – a] pyrimidin – 4 – one, Fig. (1.1.1.) , is an analytical antipsychotic drug, which blocks serotonin 5 – HI_2 and dopamine D_2 receptors and is widely used in the treatment of schizophrenia[25-28]. Several methods have been reported for the determination of risperidone in pharmaceutical dosage forms and in biological fluids including validated LC – MS / MS[29], Sensitive and liquid chromatography and tandem mass

spectrometry[30-36], IR and Raman spectroscopy and X – ray powder diffraction[37], High performance liquid chromatography and capillary electrophoresis, ^{1}H NMR spectroscopy and electro spray ionization mass spectrometry[38-43].

2. Experimental

2.1. Apparatus and Reagents

SHIMADZO UV - VISIBLE 53- spectrophotometer (Japan made) with 2 nm slit width and 1 cm quartz cell was used. The Shimadzo spectral analysis and measurement software was used for spectral data acquisition, storage and manipulation. All data treatments, calibration and prediction were carried out using the ORIGIN program for illustrating the data (Microcal software Inc.,USA 1999) package, version 6. All chemicals used are of analytical grade. Risperidone (97.98% HPLC, Powder Sigma) were dedicated from Drug Research Organization (DRO, Egypt). DDQ, Fig. (1.1.2.) (98% Aldrich), TCNQ ,Fig. (1.1.3.) (98% Aldrich), TCNE ,Fig. (1.1.4.) (97% (Fluka) and CA, Fig. (1.1.5.) (98% Aldrich).

2.1.1. Tablets

Risdal : 20 tablets produced by the Egyptian Pharmaceutical industries CO. Eipico, claimed to contain 2 mg per tablet., Psychodal : 30 tablets produced by DELTA PHARMA S. A. E, Tenth of Ramadan city, Egypt, claimed to contain 1mg per tablet and Sigmadone 10 tablets produced by SIGMA Pharmaceutical Industries, claimed to contain 3 mg per tablet.

2.2. Procedure

Standard solution of risperidone was prepared by dissolving 50 mg in acetonitrile and completing to the mark in 50 ml measuring flask.

For reagents DDQ, TCNQ, TCNE and CA, solutions of 5mg / ml were prepared by dissolving 0.25 g of each reagent in acetonitrile and the volume was completed in a 50 ml measuring flask up to the mark.

3. Results and discussion

3.1. Effect of reagent concentrations

To establish the optimum experimental conditions for the formation of RIS charge transfer complexes, the drug (100µg / ml^{-1}) was allowed to react with different volumes of the reagents (DDQ, TCNQ, TCNE and CA respectively, each 5mg ml^{-1}). The maximum absorbance was obtained with the optimum volume of 2ml for each reagent as shown in figure (1.2.).

3.2. Stochiometry of the CT complexes

The stoichiometry of the formed CT complexes was determined by applying both the molar ratio and continuous variation methods fig (1.3.). In the molar ratio method, aliquots (0.5-4ml) of the standard risperidone solution ($1x10^{-3}molL^{-1}$) were transferred into 10 ml measuring flasks followed by 1 ml of each of the reagent solution ($1x10^{-3}molL^{-1}$), the volume was completed to 10ml with acetonitrile. The absorbance of resultant CT complexes between risperidone and each of the cited reagents was measured at 843, 520, 457 and 414 nm for TCNQ, CLA, DDQ and TCNE respectively, against blank.

In the Job's method of continuous variation, both volumes of the drug and each of the reagents are continuously varied so that a total volume (1ml) is kept constant and the same procedure is applied.

3.3. Solvent Effect

Risperidone and reagents show good solubility in many solvents such as chloroform, ethanol , methanol, 1,4-dioxan, 2-propanol and acetonitrile. The value of the molar absorptivity in acetonitrile is the highest because of its high dielectric constant [43]. The solvent affects the maximum wave- length position, e.g., in case of CA the maximum wavelength was at 520 nm in acetonitrile, 533 nm in 1,4-dioxan, 538 nm in 2-propanol, 543 nm in ethanol and at 531nm in methanol, as shown in figure (1.4.).

3.4. Effect of time

Reaction time was determined by following the color devolpement starting from the moment of addition of risperidone solution to that of the reagent at room temperature. The color development was attained immediately with DDQ and CA while TCNE form intense chromogen with stable absorbance after 20 min. the absorbance of these complexes remains stable for at least 120 min fig.(4.5.1.). Risperidone-TCNQ complex is formed at 70–75°C after 20 min, while the reaction of the latter reagent is reported to take place at room temperature with other drugs. Since acetonitrile boils at 81.6°C., it was not possible to test the temperature effect over than 80 °C as shown in figures (1.5.2

3.5. Calibration Measurments

Aliquots containing different concentrations of RIS were transferred into 10 ml volumetric flasks followed by 2 ml of different reagent solutions (each 5 mg ml^{-1}) and the volume was completed to the mark with acetonitrile. The colored species were generated immediately with DDQ and CA , after 20 min with TCNE and at 20 min for TCNQ but with heating up to 75°C. The absorbance of the formed CT complexes was measured at the maximum absorbance corresponding to each reagent against the blank solution. Calibration graphs were constructed by plotting the absorbance of the formed CT complexes versus the final concentration of the drug (µg ml^{-1}).

3.6. Spectral characteristics and reaction mechanism

RIS solution in acetonitrile showed negligible absorption band at 300 nm ,while on addition of different π–acceptors (DDQ, TCNQ, TCNE and CA) to the drug solution, new characteristic bands at different absorption maxima were obtained due to the formation of CT complexes between RIS and these π acceptors fig.(4.6.). RIS, being an n– electron donor, reacts with π–acceptors giving CT complexes which dissociated to give colored free radical anions, according to the following equation.

$D + A \rightarrow DA \rightarrow D^{\bullet+} + A^{\bullet-}$ CT complexes free radical anion

The interaction of RIS with DDQ in acetonitrile at room temperature gives a red colored chromogen with absorption maxima at 457, 548 and 588 nm due to the formation of the free radical anion, the wave length 457 nm was selected because it gave high linearity. The interaction between RIS and TCNQ gives a bluish–green chromogen which exhibits strong absorption maxima at 842 and 743 nm; the wavelength 842 nm is selected as it gives higher molar absorptivity with reproducible results. These bands may be attributed to the formation of the radical anion(TCNQ•-), which was probably formed by the dissociation of an original (RIS–TCNQ) complex promoted by the high ionizing power of acetonitrile solvent . RIS–CA complex has intense absorption band at 520 nm due to the formation of the corresponding CA free radical anion. Similar mechanism can be suggested for TCNE as a yellow chromogen having two absorption maxima at 395 nm and 414 nm; in quantitative analysis, the band at 414 nm was selected fig.(1.7.)

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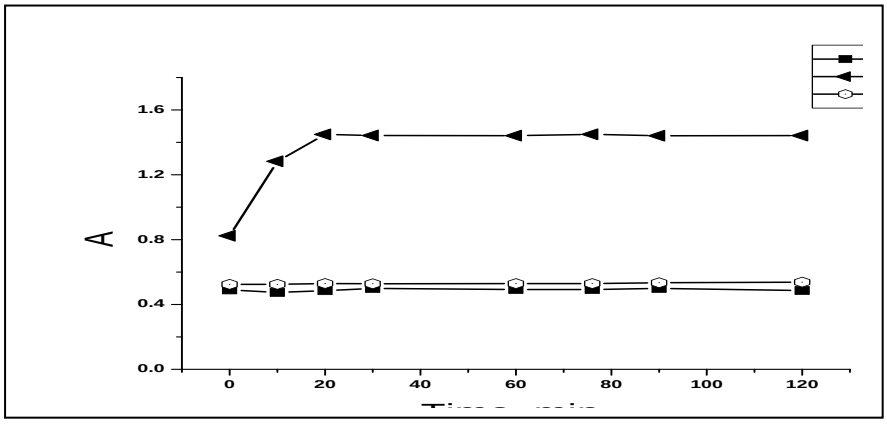

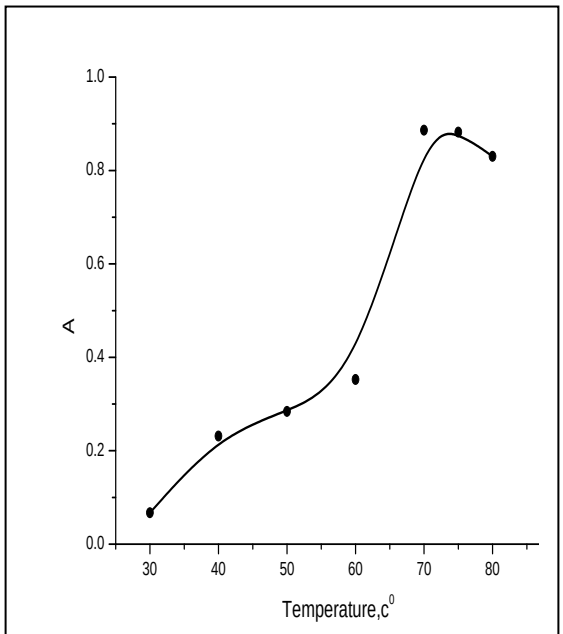

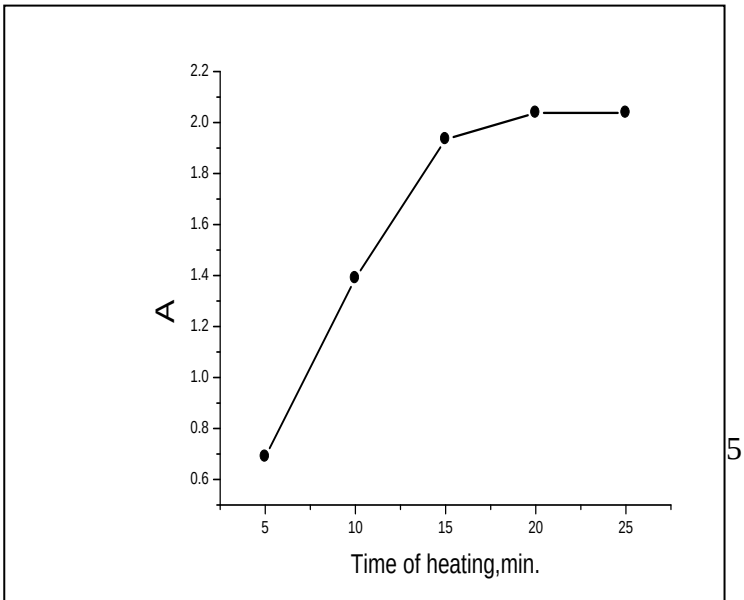

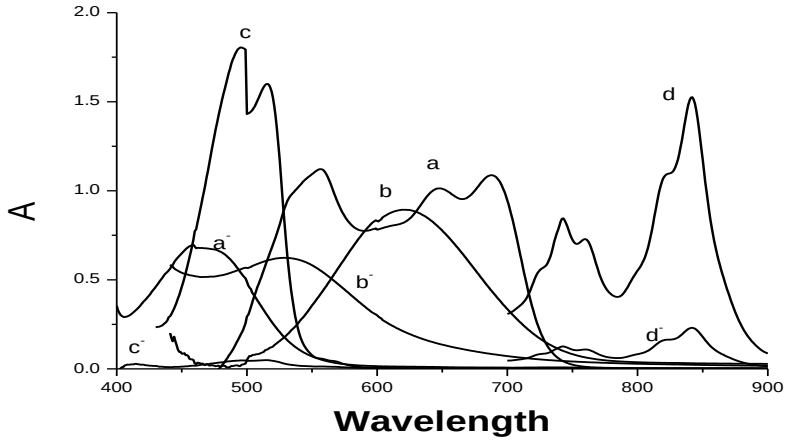

Fig. (1.6.) Absorption spectra of the RIS CT complexes with :DDQ (a), CA (b), TCNE (c) and TCNQ (d) and the corresponding reagents a^-, b^-, c^- and d^- respectively, against acetonitrile.

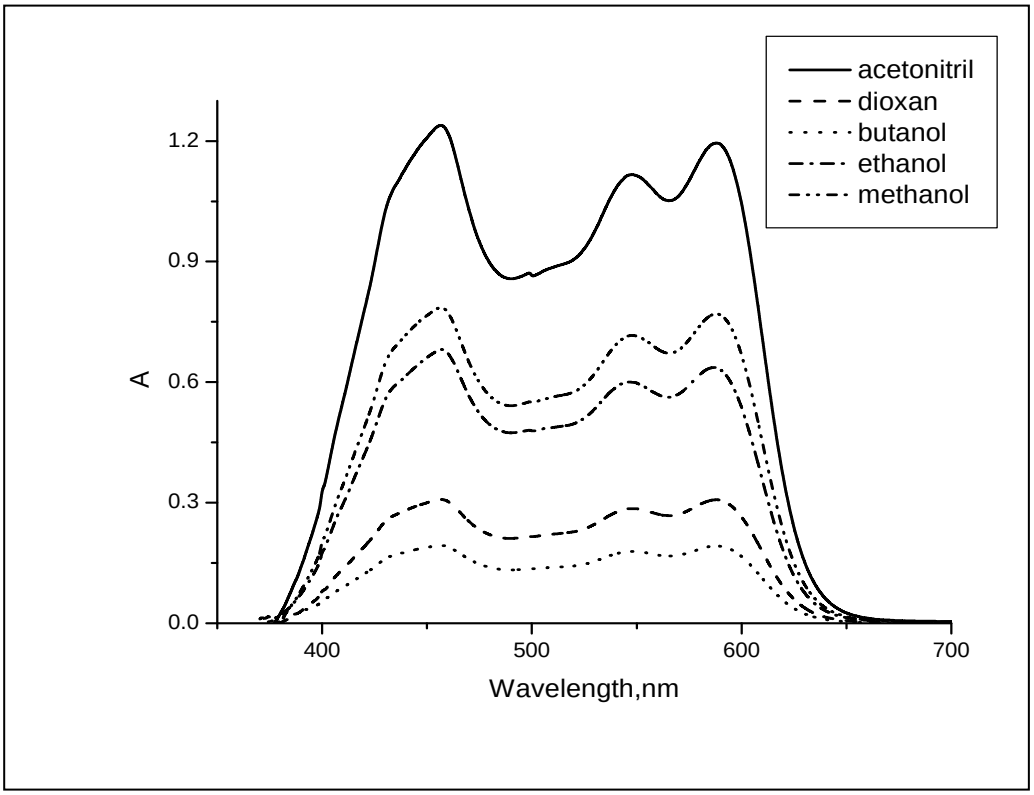

Fig.(1.4.1.) Absorption Spectra of DDQ in different solvent: acetonitrile, methanol, ethanol, 1,4- dioxin and 2- propanol.

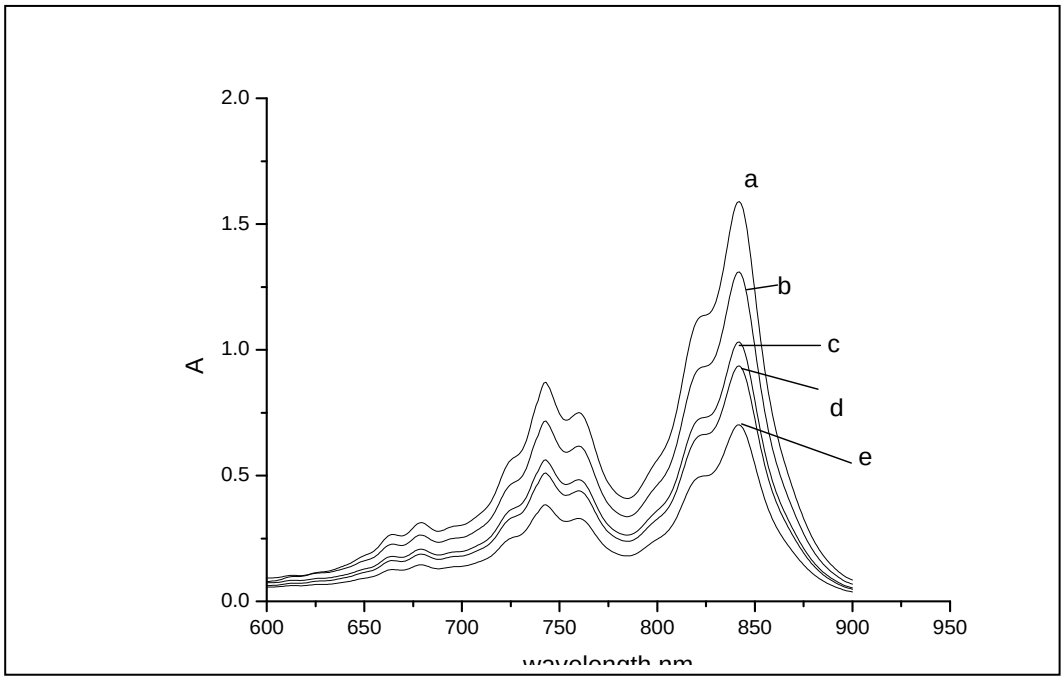

Fig. (1.4.2.) Absorption Spectra of the RIS CT Complex with TCNQ in different solvents, acetonitrile (a) , methanol (b), ethanol(c), 1,4-dioxan (d), 2- propanol(e). at 70°C.

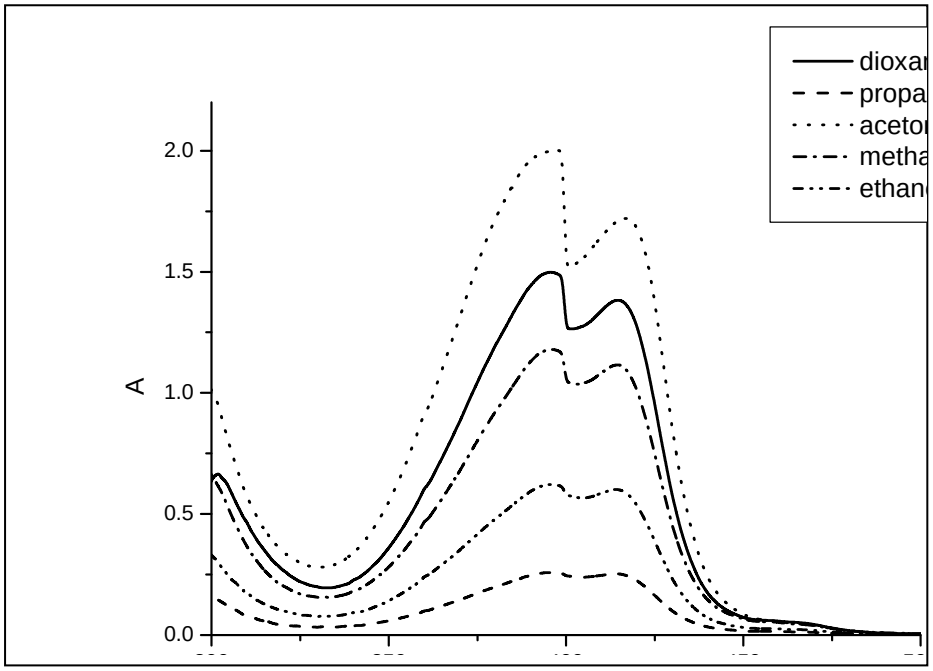

Fig. (1.4.3.) Absorption Spectra of the RIS CT Complex with TCNE in different solvents, acetonsitrile (a) , 1,4 dioxan (b), methanol(c), ethanol (d), 2-propanol(e).

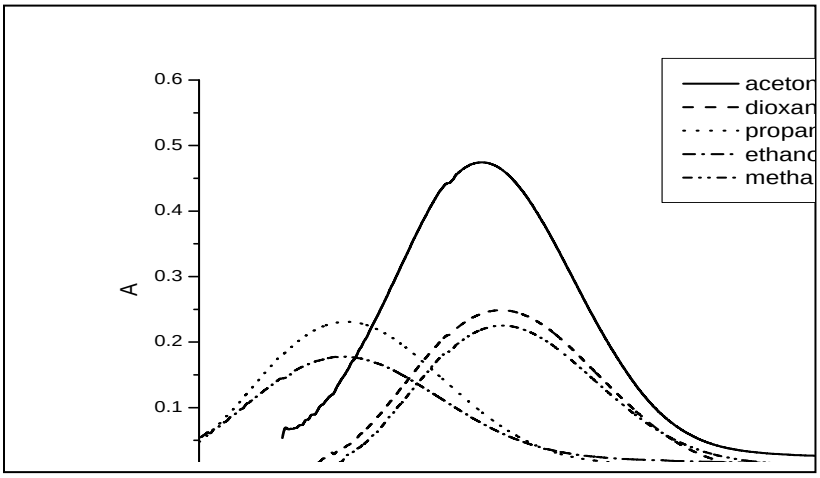

Fig. (1.4.4.) Absorption Spectra of the RIS CT Complex with CA in different solvents :(a) acetonitrile ,(b) 1,4-dioxan,(c) methanol, (d)2- propanol & (e)ethanol.

Fig. (1.3.1.) Continuous variation methods for Risperidone and different Reagents Using Job's method.

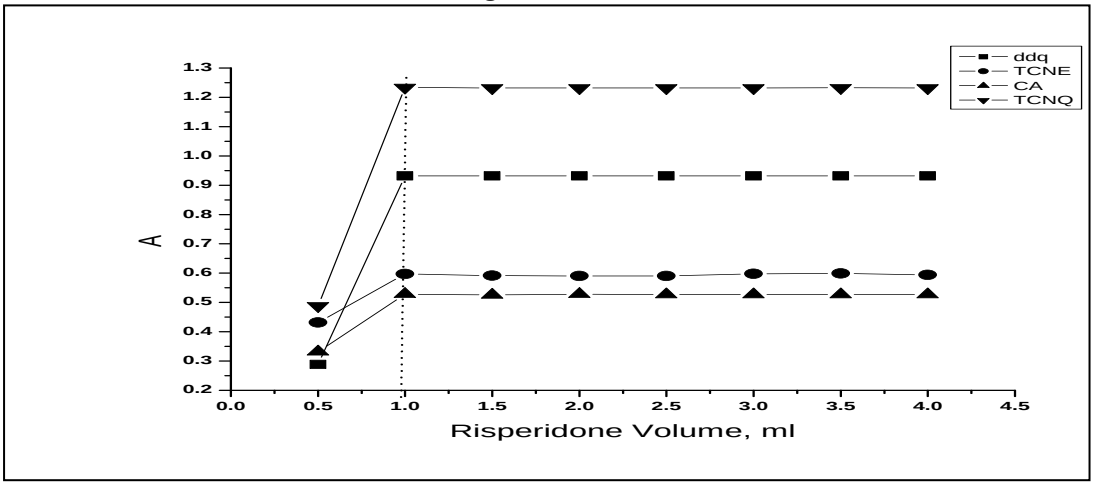

Fig. (1.3.2.) Molar ratio methods for Risperidone and the four different Reagents .

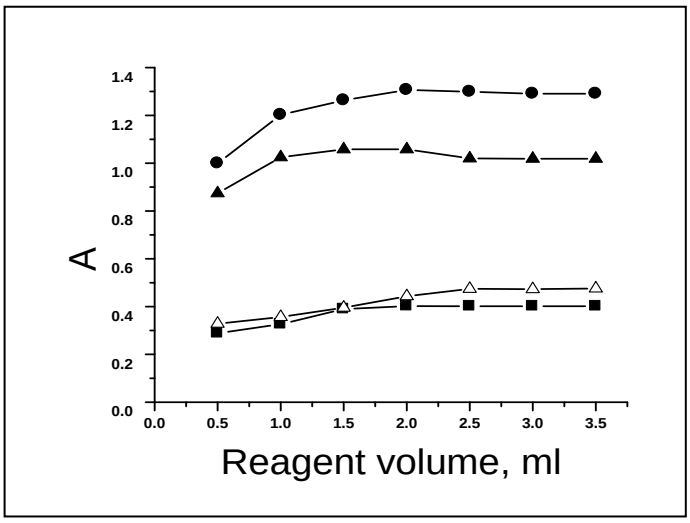

Fig. (1.2.) Effect of Reagent's Volume on the Absorbance

Table 1 Regression parameters for the four acceptors with risperidone.

	Acceptors			
	DDQ	CA	TCNE	TCNQ
Limits µgml^{-1}	8-150	25 – 250	5 – 70	10 -110
Molar absorptivity L mol^{-1} cm^{-1}	1.7x10^{6}	6.9x10^{5}	5.6x10^{6}	2.4x10^{6}
Slope ***b***	0.01057	0.00422	0.03143	0.0147
Intercept ***a***	0.0827	0.03918	-0.04081	0.1157
Corr. Coeff. ***R***	0.9995	0.99932	0.999	0.9997
S.D.	0.01274	0.01218	0.0202	0.0139
L. D*	3.62	8.66	1.93	2.85
L.Q.	12.05	28.86	6.43	9.46

The limit of detection was calculated on the basis of 3σ[43]. *

Table 2 Analysis of some pharmaceutical preparations containing risperidone .

			Acceptors			
			DDQ	CA	TCNE	TCNQ
	Risdal	Taken (µg ml^{-1})	45	95	30	55
		Found (µg ml^{-1})	43.61	93.03	30.91	52
		Recovery(%)	96.91	94.93	103.03	96.32
		*S. D.	0.42	0.47	0.36	0.43

Tablets		R.S.D.	0.97	0.51	1.2	0.82
	Sigmadone	Taken (μg ml^{-1})	61	65	20	90
		Found (μg ml^{-1})	60.68	64.69	19.58	87.31
		Recovery(%)	99.48	99.52	97.88	97.01
		*S. D.	0.35	0.33	0.41	0.39
		R.S.D.	0.58	0.51	2.1	0.45
	Psychodal	Taken (μg ml^{-1})	150	145	50	75
		Found (μg ml^{-1})	148.69	142.99	47.82	73.96
		Recovery(%)	99.11	98.61	95.64	98.61
		*S. D.	0.37	0.39	0.45	39
		R.S.D.	0.25	0.27	0.95	0.53

Average of five determinations.*

Conclusion

Charge transfer complexes method give high and sensitive results in case of risperidone and some reagents like DDQ, TCNQ, TCNE and CA.

The reaction was spontaneous in the case of DDQ and CA while with TCNE it takes place after 20 minutes and after heating for 20 min up to 75°C in case of TCNQ, the most suitable solvent was acetonitrile. The proposed method was applied for the determination of risperidone in some pharmaceutical preparations such as Risdal, Sigmadone and Psychodal.

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