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Spectrophotometric Study of Reaction Mechanism Between 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone, 7,7,8,8-Tetracyanoquinodimethane π- and Iodine σ-Acceptors and Tiapride and Their Determination in Pure and Dosage Forms

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Three simple and accurate spectrophotometric methods are presented for the determination of antipsychotic drug, tiapride in pure and in different pharmaceutical preparations. The charge transfer (CT) reactions between tiapride as electron donor and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ),7,7,8,8-tetracyanoquinodimethane (TCNQ) as π-acceptors and iodine σ-acceptor reagents have been spectrophotometrically studied. The optimum experimental conditions have been studied carefully. Beer's law is obeyed over the concentration range of 15-120, 30-140 and 20-120 μg mL^{-1} for tiapride using DDQ, TCNQ and iodine, respectively. Sandell sensitivity is found to be 0.050, 0.031 and 0.053 μg cm^{-2} for tiapiride using DDQ, TCNQ and iodine respectively, which indicate the high sensitivity of the proposed methods. The results are also confirmed by day precision of per cent recovery of 99.94-100.02, 99.91-100.4 and 99.90-100.11 % for DDQ, TCNQ and iodine methods, respectively. The data are comparable to those obtained by British and American Pharmacopeias assay for the determination of tiapride in raw materials and in pharmaceutical preparations.

Key Words: Spectrophotometry, Tiapride, 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), 7,7,8,8-Tetracyanoquinodimethane (TCNQ), Iodine, Pharmaceutical preparation.

INTRODUCTION

The charge transfer (CT) reaction had been widely studied spectrophotometrically in the determination of drugs that are easy to be determined based on the CT complex formation with some electron acceptors. The 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) and 7,7,8,8-tetracyanoquinodimethane (TCNQ) are strong electron acceptors and applied for the determination of several drugs and literature in the last decade had been mainly concentrated on CT-complexes spectral studies[1-7]. Iodine is amphoteric reagent as given by its structure due to the molecular orbital theory (MOT) and literature is scanty from works using iodine as an acceptor in drug analysis[8-12]. Tiapride is a substituted benzamide which exhibit antipsychotic, antidepressive and antiulcer properties. It is antagonist of the D_2 and D_4 brain dopamine receptor

with low frequency of extrapyramidal side effect and has been used in the treatment of depression, schizophrenia and psychopathology of senescence and gastric problems[13]. Various methods were used in determination of tiapride[14-22] but rarely depend on CT-complex formation. The chemical name of tiapride according to IUPAC is N-(2-diethylaminoethyl)-2-methoxy-5-methylsulfonylbenzamide ($C_{15}H_{24}N_2O_4S$. m.w. = 328.42)[13]. The present research aims mainly to study the reactions of DDQ, TCNQ and iodine reagents as electron acceptors with tiapride and the use of these reaction in spectrophotometric microdetermination of these drugs in pure and in some of their pharmaceutical preparations.

EXPERIMENTAL

Ashimadzu (Model 160A) UV-visible double beam spectrophotometer with 1.0 cm quartz cell was used in spectrophotometric measurements.

All chemical and solvents used were of analytical and pharmaceutical grads. Pure drug standard samples were supplied, by Memphis company, Egypt. Dosage forms of tiapride were purchased by Memphis company DDQ and TCNQ were supplied by Aldrich company, USA. Where iodine from ACF Chemic Farma, Holland. The pharmaceutical form of tiapride is tiapridal tablets (100 mg per tablet), Memphis Co. for pharmaceuticals, Egypt.

Fresh solutions of DDQ and TCNQ (1 mg mL^{-1} in acetonitrile) and iodine (0.01 M in acetonitrile) were prepared. Tiapride (1 mg mL^{-1} in acetonitrile) were prepared as stock solutions for DDQ, TNCQ and I_2 methods.

Procedure: In a 10 mL measuring flask aliquots containing 15-140 μg mL^{-1} of working solutions of tiapride were added to 1 mL of 1 mg mL^{-1} DDQ or TCNQ or to 1 mL of 10^{-3} M I_2 solution. The volume of the solutions were completed to the mark with acetonitrile and mixed well. The solutions was left to stand for 10 min at room temperature before the absorbance was measured at 463 nm for tiapride-DDQ (CT-complex) at 482 nm for tiapride-TCNQ (CT-complex) and 360 nm for tiapride-I_2 (CT-complex) respectively. The same procedures were applied for the spectrophotometric analyses of pharmaceutical dosage forms of tiapride.

RESULTS AND DISCUSSION

Absorption spectra, stoichiometry and reaction mechanism: The charge transfer-complex (tiapride-I_2) exhibited two bands at 360 or 420 nm (Fig. 1). These bands may be attributed to the charge transfer from donor amine (D) and iodine σ-acceptor leading to the formation of an ion pair, as described by **Scheme-I**. As described in literature[23].

$D + I_2 \rightarrow D–I_2$ (outer sphere complex)
$D–I_2 \rightarrow [D–I] + I^-$ (Inner sphere complex)
$[D–I]+ I^- + I_2 \rightarrow [D–I]\ I_3^-$ (Ion pair)

Scheme-I

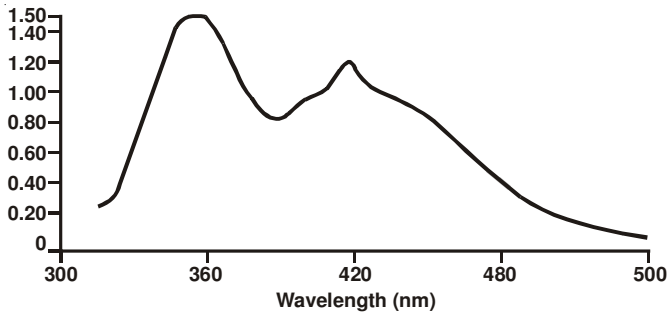


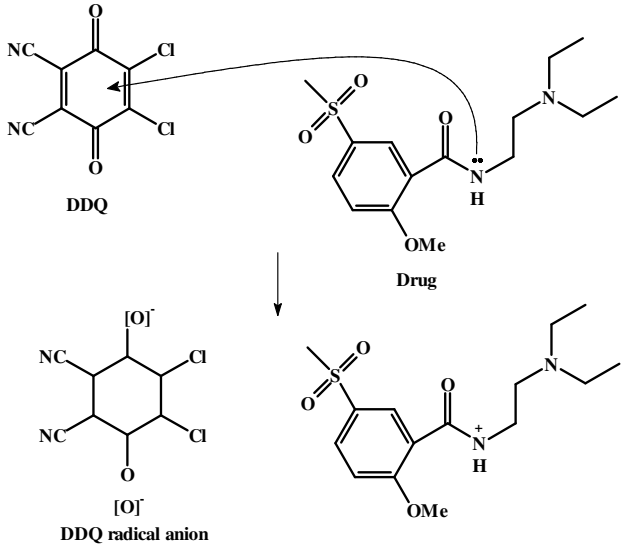
Fig. 1. Absorption spectra of charge transfer complex for tiapride with I_2 in acetonitrile

The formation of I_3^- ion which is the measured species, is due to the transformation of an 'outer sphere' to an 'inner sphere complex' liberating I^- ions that formed as a result of the reaction between iodine as σ-acceptor and tiapride as donor (**Scheme-I**). The formation of I^- initiates the reaction to its final stage to give an ion pair.

In the last few years different charge transfer complexing agent as π-acceptors A, such as DDQ and TCNQ, have been used for the pharmaceutical assay of donors (D) drugs[7,24-30]. Polar solvent as acetonitrile was reported[29,30] to promote complete transfer of charge from donor (D) to π-acceptor (A) such as DDQ resulting in complete formation of DDQ radical anion[30] $(A)^-$ as a predominant chromogen as given by the following equation:

$$\ddot{D} + A \rightarrow \underset{\text{DA complex}}{[\ddot{D} - A]} \xrightarrow{\text{polar solvent}} \underset{\text{radical ions}}{D^+ + A^-}$$

The reaction mechanism of CT complex formation between the drug under study and DDQ reagent is given by **Scheme-II**.



Scheme-II

Applying the molar ratio method[31] for the reaction of DDQ, TCNQ and iodine reagents with tiapride refer to the stoichiometry of the drug donor (D) to the reagents acceptors (A) of the ratio 1:1 (D:A). Figs. 2 and 3 show the absorption spectra of DDQ-tiapride and TCNQ-tiapride CT-complexes. Also π-π* CT complex is formed *via* the benzene ring (electron rich group) of tiapride drug and TCNQ reagent (electron acceptor)[32,33].

The effect of concentration and volume of the reagents were studied and the optimum concentration was 1 mg mL^{-1} for tiapride and the optimum volume was 1 mL. The best formation of the CT complexes were after 10 min (Figs. 4-6). The absorption spectra of CT complexes were studied in different organic solvents (acetonitrile, chloroform, acetone and toluene), the best solvent is acetonitrile and it offer the excellent solvent capacity as it gives the highest yield of DDQ radicals[34]. Acetonitrile was also considered as an ideal solvent because it offered an excellent solvating power for TCNQ reagent to give high absorbance[32,35].

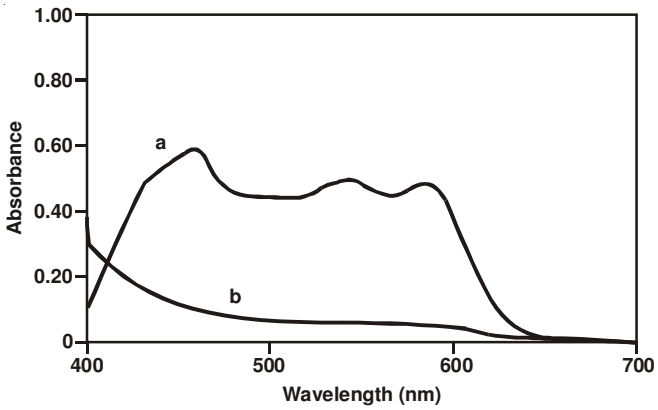


Fig. 2. Absorption spectra of (a) Tiapride-DDQ CT-complex; (b) DDQ in acetonitrile

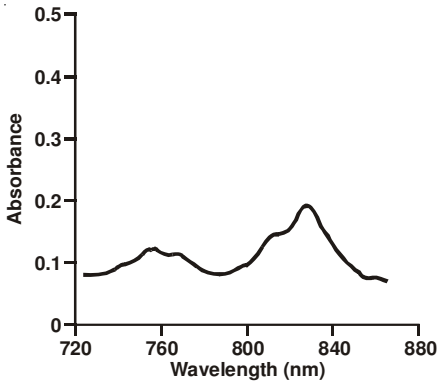


Fig. 3. Absorption spectra of charge transfer complex of tiapride with TCNQ in acetonitrial

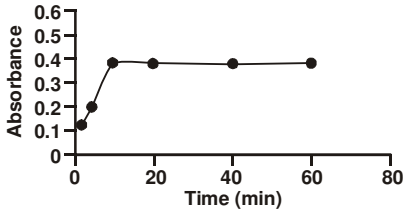


Fig. 4. Effect of time between DDQ and tiapride

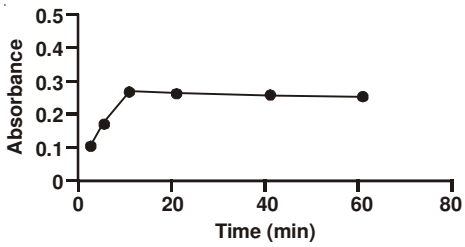


Fig. 5. Effect of time between TCNQ and tiapride

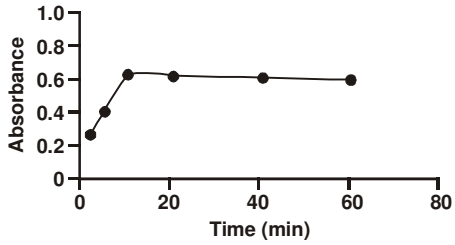


Fig. 6. Effect of time between iodine and tiapride

Calibration and precision: Typical calibration data for tiapride using DDQ, TCNQ and I_2 reagents obtained from linear regression analysis of the absorbance readings *versus* concentration of the drugs (μg mL^{-1}) were made. Beer's law limits are 15-120, 30-140 and 20-120 μg mL^{-1} for tiapride using DDQ, TCNQ and I_2 reagents, respectively. The apparent molar absorptivities of the resulting colour products CT complexes were 1×10^4, 1.18×10^4 and 1.25×10^4 L mol^{-1} cm^{-1} for tiapride using DDQ, TCNQ and I_2 reagents, respectively. The correlation coefficient of the data obtained are 0.9908, 0.9927 and 0.9969 for tiapride in DDQ, TCNQ and I_2 methods, respectively.

The mean recovery values obtained in the average 99.94-100.02, 99.91-100.04 and 99.90-100.11 % for tiapride in DDQ, TCNQ and I_2 methods, indicates the success of the applied methods in the micro-determination of tiapride in pure form. The low values of the calculated standard deviation, SD = 0.069-0.077, 0.048-0.053 and 0.072-0.080 for tiapride in DDQ, TCNQ and I_2 methods, respectively and RSD % = 0.059-0.256, 0.037-0.159 and 0.068-0.369 for tiapride in DDQ, TCNQ and I_2 methods, respectively. These values indicate the high accuracy and precision of the proposed methods. The performance of the proposed methods was assessed by comparison with the British and American Pharmacopeias[36]. Comparison through the F-test and t-test[37] showed equivalency of these methods.

Interference: Interfering materials are mainly those which causing analytical problems. Interference studies were carried out in order to investigate the effect of other ingredients. It was found that, the proposed methods can be applied to determine tiapride in various pharmaceutical preparations without any analytical problems. The tablet filler such as starch, lactose and glucose did not interfere in the proposed methods.

Application: The three proposed methods are applied for the spectrophotometric determination of tiapride in dosage forms *via* the reactions with DDQ, TCNQ and I_2 acceptors. The results obtained by the proposed methods are compared with the results of nonaqueous titrimetric method based on the titration of the drug dissolved in glacial acetic acid against perchloric acid as given in British and United States Pharmacopeias[38].

The proposed methods are more comfortable than the non-aqueous titrimetric method, since the last required high concentration of the drug while that the proposed one worked well in microconcentration ranges. The proposed method can be recommended for routine analysis in the majority of drug quality control laboratories. Another favourable characteristic of the methods is that the absorbencies of the coloured products formed are stable at least 24 h.

On comparison of the results obtained by the proposed methods with the official method[39]. Using the t-test for the accuracy and F-test for the precision assessment, the calculated values did not exceed the corresponding theoretical values (tabulated value of t-test and F-test is under confidence level 95 % = 6.39 and 2.77 for n = 5 degrees of freedom) indicating insignificant differences between the results and also refer to the robustness of the proposed procedures. The proposed methods are more accurate and of high robustness, with high recoveries amounting to 99.93-100.04 ± 0.5. The day-by-day availability of the proposed methods is studied and gives the values of between day SD and RSD for different concentrations of drug of SD = 0.069-0.077 for DDQ method, 0.048-0.053 for TCNQ method and 0.072-0.080 for iodine method and RSD = 0.059-0.256 for DDQ method, 0.073-0.159 for TCNQ method and 0.068-0.369 for iodine method, respectively. These results refer to the high accuracy, precision and robustness of the applied procedures.

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