Charge-transfer interaction between antihistamine antiallergic drugs, diphenhydramine, fexofenadine, cetirizine and two π -acceptors in pharmaceutical forms

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Abstract

Two simple and sensitive spectrophotometric techniques have been proposed for the estimation of antihistamine drugs, diphenhydramine hydrochloride (DPH), fexofenadine hydrochloride (FXO) and cetirizine dihydrochloride (CTZ) in pure forms and in their pharmaceutical forms via charge-transfer complex formation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and 7,7,8,8-tetracyanoquinodimethane (TCNQ) reagents. Spectrophotometric methods involve the addition a known excess of DDQ or TCNQ reagents to DPH, FXO and CTZ drugs in acetonitrile, followed by the measurement of the absorbance of formed CT complexes at the selected wavelength. Various variables and parameters affecting the reactions were studied and investigated. Beer's law was obeyed in the concentration ranges of 16–144, 12–120, 12–86 $\mu\text{g mL}^{-1}$ and 6–66, 24–216 and 4–68 $\mu\text{g mL}^{-1}$ for DPH, FXO and CTZ drugs using DDQ and TCNQ reagents, respectively, with correlation coefficients not less than 0.9944. The reaction stoichiometry is found to be 1:1 [drug]: [DDQ or TCNQ]. For the spectrophotometric methods, molar absorptivity, detection and quantification limits, and sandell resistance are also calculated. According to ICH guidelines, both intra-and inter-day precision and reliability were evaluated. The estimated techniques have been successfully applied in their medicinal forms to the determination of the cited drugs. The finding showed no significant difference between the estimated methods and reported methods, depended on *t* test and variance ratio. Popular pharmaceutical additives did not interfere.

Keywords Spectrophotometric · Antihistamine drugs · DDQ · TCNQ

1 Introduction

Diphenhydramine hydrochloride (DPH) (Fig. 1a) (2-(diphenylmethoxy)-N,N-dimethylethanamine) is a chemical mainly used as antihistaminic, antiemetic, sedative, and hypnotic [1]. By blocking the effect of histamine at H1 receptor sites and decreases their sensitization, DPH works. This leads to the increase of vascular smooth muscle contraction, so reducing the redness, hyperthermia

and edema that occur during an inflammatory reaction. Several techniques were published for the estimation of DPH in pharmaceutical formulations and in biological fluids including: spectrophotometry [2–5], potentiometric [6], high performance liquid chromatography [7, 8], liquid chromatography [9] and capillary electrophoresis [10, 11].

Fexofenadine hydrochloride (FXO), ($\pm$)-4-[1-hydroxy-4-(4-hydroxydiphenyl methyl)-1-piperidinyl]-butyl]- α,α -dimethyl benzene acetic acid (Fig. 1b) is a non-cardio toxic

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Fig. 1 Structural forms of the studied drugs: **a** diphenhydramine, **b** fexofenadine and **c** cetirizine

second-generation histamine H1-receptor antagonist in piperidine-class drugs used to treat hay fever symptoms. Because it does not cross the blood–brain barrier, sedation or other central nervous system effects don't occur [12]. Fexofenadine has no negative effect on the psychomotor efficiency. The substance has anti-inflammatory characteristics, which presents a modern approach to allergy therapy. For once daily prescription, FXO is suitable because it proved a safer alternative in the treatment of asthma and atopic dermatitis [13] and it is rapidly absorbed with a long duration of action. Several methods for the estimation of fexofenadine hydrochloride in pharmaceutical forms and biological fluids have been published including HPLC [14–19], spectrophotometry [20–24], spectrofluorometry [25], potentiometry [26] and capillary electrophoresis [27].

Cetirizine dihydrochloride (CTZ) (Fig. 1 c) named as 2-[2-[4-[(4-chlorophenyl) phenylmethyl] piperazin-1-yl] ethoxy]acetic acid dihydrochloride, is the second generation of histamine H1 antagonist and it shows high affinity to the histamine H1 receptors [28]. The efficacy of CTZ is demonstrated by the inhibition of allergic reactions by blocking the activity of histamine in the body and it has been used in the treating of seasonal anaphylactic rhinitis in age more than 2 years for children. Drug analysis is a serious and significant subject in many quality control steps of pharmaceutical applications. A number of analytical methods for quantification of CTZ in bulk and/or pharmaceutical forms are found in the literature. High-performance liquid chromatography (HPLC) is the most widely used technique [29, 30], liquid chromatography [31] and gas chromatography [32]. But, chromatographic methods consume time, large volumes of organic solvents and use expensive HPLC columns. Capillary electrophoresis methods also reported [33, 34], voltammetry [35, 36], potentiometric [37] and spectrophotometric techniques [38].

In this study, two simple, accurate, time saving and sensitive spectrophotometric techniques were developed to assay DPH, FXO and CTZ in pure form and their pharmaceutical preparations. The proposed methods were based on the charge transfer reaction of the cited medicaments, as n -electron donor, with DDQ and TCNQ, as π -acceptors. Literature survey did not reveal any of suggested techniques for determination of estimated drugs. Different experimental parameters affecting these reactions are optimized and then Beer's law is carried out.

2 Experimental

2.1 Apparatus

All the absorption spectral measurements were made using Shimadzu UV-160A, UV–Vis double beam spectrophotometer with scanning speed 400 nm min^{-1} and bandwidth 2 nm, equipped with 10 mm matched quartz cells.

2.2 Reagents and solutions

The reagents of analytical-reagent grade were used, and the solvents of spectroscopic grade were also used. From the Egyptian Pharmaceutical Industries Company (EIP-ICO), diphenhydramine hydrochloride (DPH), fexofenadine hydrochloride (FXO) and cetirizine dihydrochloride (CTZ) were getting. The standard solution of used drugs has been prepared as 100 mg of each drug in 100 mL of distilled water. All solutions were prepared daily. The working solution was prepared as required by suitable dilution.

of the stock solution. A stock solution of 5×10^{-3} M of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and 7,7,8,8-tetracyanoquinodimethane (TCNQ) were prepared in acetonitrile. DDQ and TCNQ were obtained from Aldrich, Sigma-Aldrich Chemie, Steinheim, Germany.

2.3 Recommended procedures

2.3.1 Preparation of cited drugs base solution

A 25 mL of standard solution of 1.0 mg mL^{-1} of the used drugs was prepared in chloroform and transferred into a 125 mL separating funnel, followed by 50 mL of 0.5 M aqueous sodium carbonate solution. These contents were mixed well in the separating funnel and shaken for 2 min. Separation of the two phases were allowed to occur and over anhydrous sodium sulphate, the chloroform layer was let to be dry and evaporated to dryness. Under distilled water, the residue was dissolved and quantitatively transferred to a volumetric flask of 100 mL. To achieve a working concentration, the volume was completed with distilled water to the limit.

2.3.2 Construction of calibration curves

According to the optimum conditions specified in Table 1, calibration curves were constructed. This achieved by transfer various aliquots of working standard solutions of the estimated drugs into separate 10 mL volumetric flasks. For this reaction, 3.0 mL of 5×10^{-3} M of each acceptor was added, and in the case of DDQ, solution leave to stand at room temperature for the optimum time and in the case of TCNQ, solution was heated on water bath to optimum temperature and heating time. Use acetonitrile solvent to make up to volume and measure the absorbance against the reagent blank at the corresponding λ_{max} . The calibration graph was prepared by plotting the measured absorbance versus drug concentration in each case. The unknown concentration was estimated from the calibration graph or calculated from the regression equation.

2.3.3 Limit of detection, and quantification

LOD is the lowest amount of analyte in the study or test sample that can be detected. LOQ is the lowest amount of analyte in the study or test sample that can be quantitatively determined by suitable precision and accuracy. By using the following equations designated by ICH guidelines, LOD and LOQ were determined.

$$\text{LOD} = 3.3 \text{ s/k} \quad (1)$$

$$\text{LOQ} = 10 \text{ s/k} \quad (2)$$

where s is the standard deviation of the absorbance measurements and k is the slope of the related calibration curve [39].

2.3.4 Accuracy and precision

To determine accuracy and precision, Intraday and inter-day analysis of the selected drugs was used. Accuracy was executed to assure the proximity of the test results obtained by the proposed methods to the exact value and precision was executed to ascertain the reproducibility of results for the suggested methods [40]. Samples were prepared in five replicates at three different concentrations within the Beer's law limits and the absorbance of each concentration was recorded in five duplicate ($n=5$). The results were reported as %RE and % RSD.

2.3.5 Stoichiometric ratio

Spectrophotometrically, by applying Job's method of continuous variation [41] and mole ratio method [42], the Stoichiometric ratio between the cited drugs and acceptors was estimated. In Job's method of continuous variations of equimolar solutions was employed: 5.0×10^{-2} M for standard solutions of DPH and each of π -acceptors were used and 5.0×10^{-3} M for standard solutions of FXO or CTZ and each of π -acceptors were used. A group of solutions were set up in Job's system of continuous variations in which the whole volume of drugs and acceptors was kept at 5.0 mL in whole volume of 10 mL. The reagents under general procedures were mixed in different ratios and completed as directed. In mole ratio method, the experiments were completed by mixing a fixed volume of the selected drugs with different volumes of each reagent separately and completed as explained under prescribed procedure.

2.3.6 Assay of pharmaceutical preparations

(i) For tablets

To calculate the average weight of one tablet of each commercial pharmaceutical form for CTZ or FXO, ten tablets were crushed, powdered, weighed out. An appropriate weight equivalent to 100 mg of the selected drugs was transferred into a 100 mL measuring flask. Approximately 25 mL of distilled water was applied and the mixture was shaken in a vigorous way for about 5 min. Then, by using distilled water, the mixture was diluted up to the mark, mixed well and filtered by filter paper. To obtain the working concentrations, a proportion of this solution was

Fig. 2 Absorption spectra of charge-transfer complexes of FXO with **a** DDQ and **b** TCNQ reagents in acetonitrile

Fig. 3 Effect of different solvents on color intensity of CT-complexes with DDQ, and TCNQ

diluted appropriately and analyzed as explained under estimated procedure.

(ii) For syrup

The content of five syrup bottles of each (Diphen syrup, 14 mg/5 mL) of DPH and (histazine-1 syrup, 5 mg/5 mL) of CTZ were pooled and mixed. An accurately measured volume of the mixed syrup equal to 100 mg of the selected drugs was transferred quantitatively into a separating funnel and treated as explained under estimated procedure.

3 Results and discussion

Due to the interaction of n -electron donor (DPH, FXO and CTZ drugs) with π -acceptors (DDQ and TCNQ) the formation of charge transfer complex take place, forming a

colored charge transfer complexes with low molar absorptivity which created in non-polar solvent. In contrast, a full electron transfer from drugs (D), (n-electron donor), to the acceptor moiety (A) (π -acceptors) take place in polar solvents such as acetonitrile with the construct of strong colored radical ions with high molar absorptivity values, according the next equation:

Fig. 4 Effect of temperature (**a**, **b**) and heating time (**c**) on the absorbance of CT-complexes of DPH, FXO and CTZ with **a** DDQ ($\lambda_{\text{max}} = 460$ nm), **b** TCNQ ($\lambda_{\text{max}} = 840$ nm) reagents in acetonitrile

Acetonitrile (polar solvent) has high degree of ionizing power [43] which confirmed the separation of the donor-acceptor complex (D–A). The apparent color complexes have absorption maxima at 460 and 840 nm for DDQ and TCNQ separately, (Fig. 2).

3.1 Effect of solvents

DDQ and TCNQ reagents reacted with DPH, FXO and CTZ drugs in different solvents in order to select the appropriate solvent for CT complex formation. Water, acetonitrile, acetone, ethanol, ethyl acetate, methanol and dimethyl-formamide, were these solvents. The ideal solvent for that reaction was acetonitrile with its capacity for DDQ and TCNQ and by high ϵ values; it gives the highest yield of the radical anion as indicated in (Fig. 3). This is because it has the high dielectric constant of all solvents examined; which facilitate the dissociation of the original CT complex to radical ions i.e. the dissociation of donor–acceptor complex is enhanced by solvent's high ionizing power [44].

Fig. 5 Effect of time on the absorbance of CT complexes of DPH, FXO and CTZ with **a** DDQ and **b** TCNQ reagents in acetonitrile

Fig. 6 Continuous variation plot of the reaction products of the studied drugs with: **a** DDQ and **b** TCNQ

3.2 Effect of reagent concentration

The drugs were allowed to react with different volumes of the reagents (0.5–4.0 mL of 5.0×10^{-3} M of both DDQ and TCNQ) to establish optimal concentrations of the reagents for the sensitive and rapid formation of the CT-complexes. In both the cases, maximum and minimum absorbance values were obtained for sample and blank only when 3.0 mL of the reagent was used, respectively. Thus, 3 mL was used throughout the analysis as the optimum volume of each reagent in a total volume of 10 mL.

3.3 Effect of reaction time and temperature

The optimum time was determined by noticed the color obtained at room temperature (25 ± 2 °C). Complete color achievement was achieved instantaneously with DDQ (Fig. 4a). Because at room temperature the drug reaction with TCNQ was sluggish, only a pale color emerged and full color production was achieved after 2 h, heating was

Fig. 7 Mole ratio plot of the reaction products of the studied drugs with: **a** DDQ and **b** TCNQ

used. The effect of temperature was studied in the range of 25–80 °C on the formed complex, (Fig. 4b). The results showed full color development at 60 °C for 40 min, 70 °C for 50 min and 80 °C for 30 min for DPH, FXO and CTZ, respectively, (Fig. 4c). As shown in Fig. 5, the formed CT-complexes remained stable at room temperature for DDQ at least 60 min and 90 min for TCNQ.

3.4 Stability constants of CT-complexes

By using the Benesi–Hildebrand equation [45], the relative stability constants of the complexes with the two reagents are estimated. The logarithmic stability constants values were 2.93, 2.91, 2.94 and 2.83, 2.89, 2.86 for DDQ and TCNQ complexes, separately.

3.5 Stoichiometric ratio

The stoichiometric reaction between the cited drugs and DDQ or TCNQ was determined spectrophotometrically, by

Scheme 1 Probable reaction mechanisms for FXO with TCNQ as π -acceptors as example for the proposed methods

applying Job's continuous variation and mole ratio methods. The results as in Figs. 6, 7 showed that, the relation between the examined drugs and each one of π -acceptors was found to be 1:1. Although the drug has two nitrogen atoms, only one nitrogen atom will be used in the formation of CT complexes. Depended on that, a possible path of reaction is proposed and shown in Schemes 1 and 2 for the formation of the CT complex.

3.6 Validation of the proposed method

The methods developed are confirmed in accordance with linearity, accuracy and precision, detection limit and quantification and according to the rules set by the International Conference on Harmonization ICH Q2 (R1) [46].

3.6.1 Linearity, detection, and quantitation limits

The relationship between absorbance and concentration was quite linear in the concentration ranges given in Table 1 based on the estimated experimental parameters (Fig. 8). Table 1 summarizes the values of intercept (a), slope (b), correlation coefficient (r), molar absorptivity (e), and sandell sensitivity. The detection limit (LOD) and quantification limit (LOQ) were calculated as listed in Table 1.

3.6.2 Accuracy and precision

The accuracy and precision of the proposed spectrophotometric method were tested by performing five times analyses on drug solutions for pure DPH, FXO and CTZ at three

Scheme 2 Probable reaction mechanisms for FXO with DDQ as π -acceptors as example for the proposed methods

Fig. 8 Calibration graphs for determination of the studied drugs with **a** DDQ and **b** TCNQ

different concentration levels within the working range Table 2 calculated the percentage relative standard deviation (RSD %) as accuracy and relative error (RE) as accuracy of the estimated spectrophotometric methods. The test of intra- and inter-day accuracy and precision indicate that the estimated techniques have good repeatability and reproducibility as shown in Table 2.

3.6.3 Analytical application

The estimated methods have been applied to pharmaceutical form which commercially available to quantify the cited drugs. The results obtained were compared with those by reference methods [5, 23, 24]. The statistical analysis of the results detected no significant difference in the performance of the proposed methods and the reported methods by the Student's *t* value and variance ratio *F* value. The results of this study are given in Tables 3 and 4.

Table 1 Quantification parameters for the formed CT-complexes

Parameters	DDQ			TCNQ		
	DPH	FXO	CTZ	DPH	FXO	CTZ
$\lambda_{\max}$ (nm)	460	460	460	840	840	840
Temp (°C)	25 ± 2	25 ± 2	25 ± 2	60	70	80
Heating time (min)	5	5	5	40	50	30
Beer's law limit ($\mu\text{g mL}^{-1}$)	16–144	12–120	12–86	6–66	24–216	4–68
Molar absorptivity ($\text{L mol}^{-1} \text{cm}^{-1} \times 10^3$)	2.50	6.18	7.28	5.52	3.17	5.88
Sandell's sensitivity (ng cm^{-2})	116.60	87.02	63.42	52.84	109.81	78.52
Correlation coefficient (<i>r</i>)	0.9987	0.9986	0.9994	0.9944	0.9998	0.9983
Linear regression equation ^a	$A = a + bC$					
Intercept (<i>a</i>)	0.08	0.02	0.01	0.09	0.16	0.12
Slope (<i>b</i>)	8.14×10^{-3}	8.61×10^{-3}	1.17×10^{-4}	1.68×10^{-4}	4.90×10^{-3}	1.12×10^{-4}
$S_{y/x}$	1.35×10^{-4}	1.30×10^{-4}	5.21×10^{-3}	2.24×10^{-4}	4.29×10^{-3}	1.09×10^{-4}
S.D. of slope (S_b)	2.03×10^{-4}	2.59×10^{-4}	2.07×10^{-4}	8.93×10^{-4}	4.28×10^{-4}	3.28×10^{-4}
S.D. of intercept (S_a)	4.64×10^{-3}	4.45×10^{-3}	2.29×10^{-3}	7.66×10^{-3}	1.47×10^{-3}	3.21×10^{-3}
LOD ($\mu\text{g mL}^{-1}$)	1.08	1.03	0.76	0.56	1.93	0.84
LOQ ($\mu\text{g mL}^{-1}$)	3.30	3.12	2.29	1.70	5.86	2.55
Log stability constant (<i>K</i>) (L mol^{-1})	2.93	2.91	2.94	2.83	2.89	2.86
Standard free energy (ΔG) (kJ mol^{-1})	-2.00×10^3	-3.97×10^3	-2.02×10^3	-4.30×10^3	-4.57×10^3	-4.06×10^3

^a $A = a + bC$, where *A* is the absorbance, *C* is the concentration in $\mu\text{g mL}^{-1}$, *a* is an intercept, *b* is a slope

^bLimit of quantification and detection is calculated according to the ICH guidelines

Table 2 Evaluation of intra-day and inter-day accuracy and precision

Drugs	Drug taken ($\mu\text{g mL}^{-1}$) DDQ	Recovery ^a (%)	RSD (%)	RE (%)	Drug taken ($\mu\text{g mL}^{-1}$) TCNQ	Recovery ^a (%)	RSD (%)	RE (%)
Intra								
DPH	32	99.99	0.63	-3.12×10^{-3}	12	99.99	0.69	-4.33×10^{-3}
	32	99.99	0.29	-1.56×10^{-3}	30	99.99	0.25	-3.33×10^{-3}
	64	99.99	0.18	-1.04×10^{-3}	42	99.99	0.21	-2.38×10^{-3}
FXO	96	99.99	1.31	-4.17×10^{-3}	24	100.00	0.32	Zero
	24	99.99	0.26	-2.08×10^{-3}	72	99.99	0.44	-1.39×10^{-3}
	48	99.99	0.24	-1.39×10^{-4}	120	99.99	0.17	-7.33×10^{-3}
CTZ	72	99.99	0.80	-5.56×10^{-3}	12	99.99	0.53	-5.33×10^{-3}
	18	99.99	0.48	-3.33×10^{-3}	28	99.99	0.69	-3.57×10^{-3}
	30	99.99	0.32	-2.08×10^{-3}	52	99.99	0.17	-1.92×10^{-3}
Inter								
DPH	32	99.99	0.39	-3.12×10^{-3}	12	99.99	0.53	-3.11×10^{-3}
	64	99.99	0.21	-1.56×10^{-3}	30	99.99	0.30	-4.13×10^{-3}
	96	100.00	0.13	Zero	42	99.99	0.15	-1.98×10^{-3}
FXO	24	100.00	0.72	Zero	24	99.99	0.41	-4.17×10^{-3}
	48	99.99	0.26	-2.08×10^{-3}	72	99.99	0.28	-2.13×10^{-3}
	72	99.99	0.22	-1.39×10^{-3}	120	99.99	0.38	-5.24×10^{-3}
CTZ	18	99.99	0.69	-5.56×10^{-3}	12	99.99	0.43	-4.67×10^{-3}
	30	99.99	0.48	-3.33×10^{-3}	28	99.99	0.35	-2.87×10^{-3}
	48	99.99	0.20	-2.08×10^{-3}	52	99.99	0.19	-2.14×10^{-3}

^aMean value of five determinations, %RE: percent relative error, %RSD: relative standard deviation

Table 3 Recovery of the studied drugs in formulations using DDQ

Drug formulations	Drug taken ($\mu\text{g mL}^{-1}$)	Drug found ($\mu\text{g mL}^{-1}$)	Recovery ^a (%)	RSD ^b (%)	RE ^c (%)	Reported methods
Diphensyrup ^d	32	32	100.00	0.38	Zero	
14 mg/5 mL	64	63.99	99.99	0.25	-1.56×10^{-3}	
	96	95.99	99.99	0.13	-1.04×10^{-3}	
Recovery $\pm$ RSD			99.99 $\pm$ 0.25			100.00 $\pm$ 0.83
t test			0.50			
F test			0.68			
Allerfen 180 mg/tablet ^e	24	24	100.00	1.05	Zero	
	48	47.99	99.99	0.65	-2.08×10^{-3}	
	72	72	100.00	0.17	Zero	
Recovery $\pm$ RSD			99.99 $\pm$ 0.62			100.00 $\pm$ 2.31
t test			0.39			
F test			0.68			
Zyrtec 10 mg/tablet ^f	18	17.99	99.99	0.49	-5.56×10^{-3}	
	30	29.99	99.99	0.33	-3.33×10^{-3}	
	48	48.01	100.02	0.23	15.62×10^{-3}	
Recovery $\pm$ RSD			100.0 $\pm$ 0.35			100.01 $\pm$ 0.84
t test			0.39			
F test			0.90			
Histazine-1 syrup 5 mg/5 mL ^g	18	17.99	99.99	0.47	-5.56×10^{-3}	
	30	29.99	99.99	0.34	-3.33×10^{-3}	
	48	47.99	99.99	0.22	-2.08×10^{-3}	
Recovery $\pm$ RSD			99.99 $\pm$ 0.34			100.01 $\pm$ 0.84
t test			0.40			
F test			0.93			

^aMean value of five determinations^bRSD relative standard deviation^cRE relative error^dProduced by Egyptian Int. Pharmaceutical Industries Co. (EIPICO) 10th of Ramadan, Egypt^eProduced by Amoun Pharmaceutical Co El Obour city, Cairo, Egypt^fProduced by Glaxosmithkline, Cairo, under license from: UCB, Belgium^gProduced by Amriya for pharmaceutical industries Alex., Egypt

Table 4 Recovery of the studied drugs in formulations using TCNQ

Drug formulations	Drug taken ($\mu\text{g mL}^{-1}$)	Drug found ($\mu\text{g mL}^{-1}$)	Recovery ^a (%)	RSD ^b (%)	RE ^c (%)	Reported methods
Diphensyrup ^d	12	12	100.00	0.66	Zero	
14 mg/5 mL	30	29.99	99.99	0.43	-3.33×10^{-3}	
	42	41.99	99.99	0.22	-2.38×10^{-3}	
Recovery $\pm$ RSD			99.99 $\pm$ 0.44			100.00 $\pm$ 0.83
t test			0.43			
F test			0.54			
Allerfen 180 mg/tablet ^e	24	23.99	99.99	0.50	-4.17×10^{-3}	
	72	72	100.00	0.44	Zero	
	120	119.99	99.99	2.50	-8.33×10^{-4}	
Recovery $\pm$ RSD			99.99 $\pm$ 1.15			100.00 $\pm$ 2.31
t test			0.48			
F test			0.71			
Zyrtec 10 mg/tablet ^f	12	11.99	99.99	0.55	-8.33×10^{-3}	
	28	28	100.00	0.26	Zero	
	52	51.99	99.99	0.24	-1.92×10^{-3}	
Recovery $\pm$ RSD			99.99 $\pm$ 0.35			100.01 $\pm$ 0.84
t test			0.44			
F test			0.86			
Histazine-1 syrup 5 mg/5 mL ^g	12	11.99	99.99	0.41	-8.33×10^{-3}	
	28	27.99	99.99	0.38	-3.57×10^{-3}	
	52	51.99	99.99	0.19	-1.92×10^{-3}	
Recovery $\pm$ RSD			99.99 $\pm$ 0.33			100.01 $\pm$ 0.84
t test			0.44			
F test			0.90			

^aMean value of five determinations^bRSD relative standard deviation^cRE relative error^dProduced by Egyptian Int. Pharmaceutical Industries Co. (EIPICO) 10th of Ramadan, Egypt^eProduced by Amoun Pharmaceutical Co El Obour city, Cairo, Egypt^fProduced by Glaxosmithkline, Cairo, under license from: UCB, Belgium^gProduced by Amriya for pharmaceutical industries Alex., Egypt

4 Conclusions

1. This study explained the development and validation of spectrophotometric analysis depended on their CT reaction with DDQ and TCNQ reagents for the estimation of DPH, FXO and CTZ drugs.
2. These methods were simple, economical, accurate, sensitive, time-saving and environmental friendly which applied in acetonitrile to form CT complexes.
3. The main advantage of the estimated methods is their availability in pure form and formulations for routine quality control of the drug without fear of contamination caused by the additives supposed to be present in formulations.

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Compliance with ethical standards

Conflict of interest The authors have declared no conflict of interest.

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