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The Use of Green Spectroscopy for Analysis of Quetiapine

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Abstract

Three green (eco-friendly), inexpensive and simple spectrophotometric methods for quetiapine fumarate (QTF) analysis have been developed and validated. Method I is based on the measurement of the oxidation product of QTF at 610 nm after the reaction with potassium permanganate. Potassium permanganate was used as oxidant. Method II depends on oxidation of the cited drug with ceric ammonium sulfate where the decrease in absorption intensity at 315 nm was measured quantitively. Method III involves complexation of the studied analyte with 2´,7´-bis (acetoxymercury) fluorescein leading to a quantitative decrease in the absorption intensity of the complexing reagent at 502 nm. Different reaction conditions affecting intensity of measurement were carefully studied, optimized and validated. In all proposed methods, no need for extraction procedures and there were linear relationships between the absorbance readings and concentrations of QTF in the range of 5-35, 1-6 and 30-100 µg/mL with LOD values 1.11, 0.12 and 2.68 µg/mL for methods I, II and III respectively. The suggested methods were successfully applied to QTF analysis in pure form and in drug tablets.

Keywords: Quetiapine; Spectroscopic determination; Green method; Permanganate; Ceric; Acetoxymercury fluorescein.

1. Introduction

Quetiapine fumarate (QTF) (Figure S1) is a dibenzothiazepine atypical antipsychotic which used for treatment of schizophrenia [1]. It was recently considered as an official drug in BP 2016 and USP 38. QTF was analyzed by direct UV spectrophotometric measurement in different solvent media [2-7] and second order derivative measurement [8]. Color-producing reactions include the ion-pair complexation with sulphonthalein acidic dyes [9, 10], wool fast blue [11], quinoline yellow dye [12], calmagite [13], ion-association complex with tropaeoline ooo and naphthol blue black [14] and charge transfer complexation reactions [15]. Oxidation based spectrophotometric methods involve using potassium dichromate [16] and known excess of potassium permanganate followed by estimating the unreacted reagent with amaranth dye [17]. However, all these methods used dangerous chemicals which affect the environment and also were suffer from

Therefore, it was necessary to develop green, simple and reliable spectrophotometric methods for the analysis of QTF in bulk powder (drug substance) and in its tablets (drug product). QTF chemical structure showed oxidizable groups. Therefore, potassium permanganate, $KMnO_4$, (method I) and ceric ammonium sulfate, $(NH_4)_4Ce(SO_4)_4$ $2H_2O$, (method II) were tested for their oxidizing effect on QTF. $KMnO_4$ reacted with QTF in strong alkaline medium causing conversion of violet color of potassium permanganate to green color of managante

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species. On the other hand, ceric ammonium sulfate reaction was preferred in strong acidic medium (H_2SO_4) causing decrease in intensity of the yellow color of ceric solution. Another advantage of QTF chemical structure is the presence of sulfur atom. Therefore, Acetoxy mercury fluorescein (AMF) (method III) reaction with QTF has been attempted and the decrease in absorbance of AMF occurs upon reaction with the drug was monitored. All the parameters were investigated to obtain maximum sensitivity. All suggested methods were validated and successfully applied to QTF preparation.

2. Experimental

2.1. Instrumentation:

Shimadzu UV spectrophotometer (UV-1800) was used for all spectrophotometric measurements using 1-cm quartz cells.

2.2. Materials and reagents:

Quetiapine fumarate was provided by Medizen Pharmaceutical Industries, Alexandria, Egypt (99.80%). All chemicals used were of analytical reagents grade. Methanol was obtained from Fisher Scientific, Loughborough, UK. Ceric ammonium sulfate was obtained from Nice Chemicals, Kerala, India. Boric acid, potassium permanganate and NaOH were obtained from El-Nasr Chemical Co., Egypt. H_2SO_4 (99.5%) was provided by S.D. Fine Chemicals Limited, India, and high purity distilled water (DW) was used.

2.3. Preparation of Reagents:

Aqueous solutions of 0.1 M boric acid, 10% H_2SO_4 and 0.1 M NaOH were separately prepared using DW. To prepare 0.005 M potassium permanganate, 80 mg of potassium permanganate was dissolved in 60 mL DW; finally, the volume was made up to 100 mL using DW. Also, a ceric ammonium sulfate solution (2.3×10^{-3} M) was prepared by accurate weighting of 37.5 mg of ceric ammonium sulfate which then dissolved in 10% H_2SO_4; finally, the volume was made up to 250 mL using the same solvent. To prepare 10^{-4} M solution of acetoxymercury fluorescein (AMF); 82.3 mg of AMF which was dissolved in few milliliters of 0.1 M NaOH, then 100 mL 0.1 M boric acid were added. Finally DW was added to complete the volume to 1 L. NaOH, 0.5 M solution was prepared by weighting of 2 g of NaOH which was dissolved in 100 mL DW. Finally, H_2SO_4 solution (2 M) was prepared by adding slowly a volume of 27 mL of concentrated H_2SO_4 to 250 mL DW.

2.4. Pharmaceutical preparations:

Seroquel 100® tablets (labeled to contain 115.14 mg of quetiapine fumarate manufactured by AstraZeneca Pharmaceuticals, Egypt, under license of AstraZeneca UK) and Quitapex 100® tablets (labeled to contain 115.14 mg quetiapine fumarate manufactured by Apex pharma for pharmaceuticals & medical appliances, Egypt) were obtained from the local market.

2.5. Preparation of QTF Stock Solutions:

Hundred milligrams of QTF were quantitatively transferred into a 100 mL volumetric flask and DW (60 mL) was added as a solvent. The resulting solution was diluted to the mark with DW to provide a stock standard solution (1000 µg/mL). Serial dilution with DW was used to get 0.1 mg/mL (100 µg/mL) (stock solution for methods I and II) and 0.5 mg/mL (500 µg/mL) (stock solution for method III). The prepared stock solutions were stored refrigerated at 4 °C.

2.6. General Procedure:

2.6.1. Method I (reaction with $KMnO_4$)

Volumes of 3 mL of $KMnO_4$ were pipetted into a group of volumetric flasks (10 mL). Then, 2 mL NaOH solution (0.5 M) were added. Then accurate volumes (0.5-3.5 mL) of QTF stock solution (100 µg/mL) were added to produce concentration levels in the range of 5-35 µg/mL. The contents of the flasks were mixed, and the reaction mixtures were kept for 50 min at room temperature (25 ± 5°C). Then, DW was added to volume. Finally, the absorbance readings were taken at λ_{max} 610 nm against blank.

2.6.2. Method II (reaction with ceric ammonium sulfate)

Volumes of 1.3 mL of ceric ammonium sulfate were pipetted into a group of volumetric flasks (10 mL). Then, half milliliter of H_2SO_4 solution (2 M) was added. Then 0.1-0.6 mL of QTF solution (100 µg/mL) were added to produce concentration levels

in the range of 1-6 µg/mL. Flasks contents were mixed, and then transferred to water bath at 90 °C for 50 min, followed by dilution with DW to volume. The difference in absorbance was monitored at 315 nm against blank.

2.6.3. Method III (reaction with AMF)

Volumes of 2.3 mL of AMF were pipetted into a group of volumetric flasks (10 mL). Then 0.6 - 2 mL of QTF solution (500 µg/mL) were added to yield concentration levels in the range of 30-100 µg/mL. Then, methanol (HPLC grade) was used to dilute the flasks contents to volume. The absorbance readings were taken at λ_{max} 502 nm against the reagent alone.

In method I, the calibration plots were constructed between the produced absorbance readings against the corresponding concentrations. While in method II and II, the calibration plots were constructed between the decrease in absorbance readings against the corresponding concentrations.

2.7. Tablet Extraction Procedure

The developed methods were applied to QTF analysis in Quitapex® tablets and Seroquel® tablets which are labeled to contain 115.14 mg quetiapine fumarate salt per tablet equivalent to 100 mg quetiapine base. An equivalent weight to 100 mg QTF was added to 60 mL DW. Then the flask was vigorously shaken for 10 min. After that, the obtained suspension was filtered by the use of Whatman® filter paper into a hundred milliliters volumetric flask. Then, two 10 mL DW were added successively to the obtained residue. Then, the washings were mixed with the filtrate. Then, the obtained solution was completed to the mark with same solvent to obtain 1000 µg/mL QTF. The prepared stock sample solution (1000 µg/mL) was diluted with the DW to obtain 100 µg/mL (this solution was used in methods I and II) and 500 µg/mL (this solution was used in method III). These solutions were used to get the concentrations in the used linearity ranges (Table 1). Ten milliliters volumetric flasks were used for the general procedures.

3. Results and discussion

3.1. Spectral characteristics of the proposed colorimetric procedures

QTF shows UV spectrum in the range 200-350 nm with a peak at 290 nm (Figure S2 in supplementary file). Three color producing proposed methods were validated to get green QTF assay in different matrices. Obviously, QTF bears several functional groups susceptible to oxidation: sulfur group, tertiary amine group, primary alcohol group and possibly the fumarate salt itself.

In **method I**, preliminary trials revealed that QTF is readily oxidizable with $KMnO_4$ in alkaline medium (NaOH) at ambient temperature with the formation of the green manganate species which absorbs maximally at 610 nm. This reaction provides clear bathochromic shifted measurement where permanganate itself shows maximum absorption at 525 nm (Figure S3 in supplementary file). The intensity of green color is directly proportional to concentration of QTF. Figure 1 illustrates absorbance curves of serial concentrations of QTF after treatment with alkaline permanganate reagent.

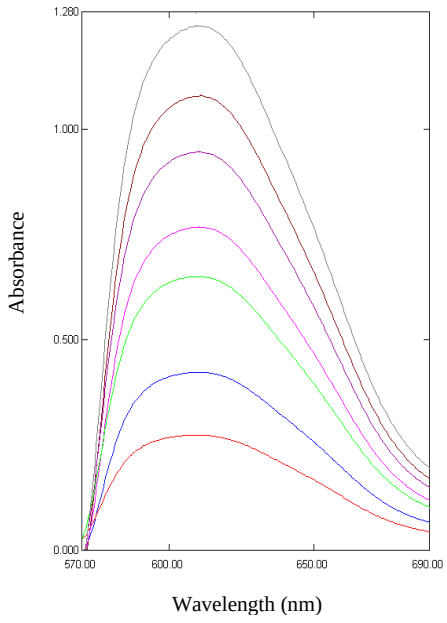

Figure 1: Absorption spectra of the reaction product of 5, 10, 15, 20, 25, 30 and 35 µg/mL of QTF with potassium permanganate in alkaline medium.

In **method II**, being a strong oxidizing agent, ceric ammonium sulfate reacts with QTF in strong acidic medium where the yellow cerium (IV) ions are reduced into the colorless cerium (III) ions with the overall decrease in intensity of the yellow color which can be measured at 315 nm (Figure S4 in supplementary file). The reaction was followed at different temperatures and it was

found that increasing temperature up to 90 °C shows significant improvement in sensitivity therefore the reaction was done at 90 °C. The decrease in color was used for measurement of concentration of QTF. Figure 2 shows absorbance of serial concentrations of QTF after treatment with ceric reagent in acidic medium.

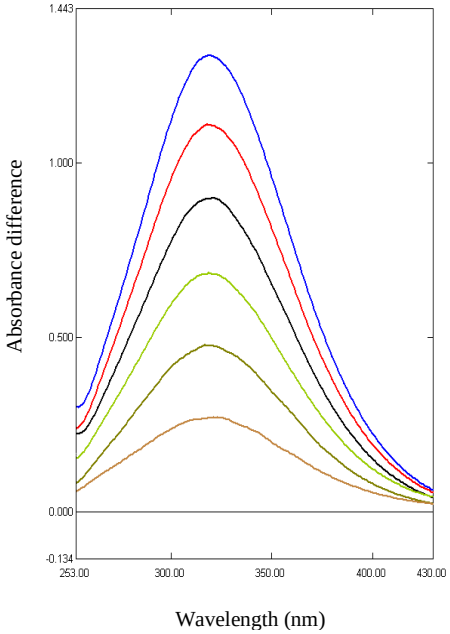

Figure 2: Absorption spectra of the reaction product of 1, 2, 3, 4, 5 and 6 µg/mL QTF with ceric ammonium sulfate.

Finally, AMF used in **method III** reacts with QTF and a decrease in absorbance of AMF at 502 nm occurs (Figure S5 in supplementary file). It was found that the decrease in absorbance at the 502 nm was proportional to QTF concentration (Figure 3). It is considered as complex formation reaction [18] in which ligand exchange is assumed to occur at the Hg atom of the reagent which shows strong affinity to compounds containing sulfhydril group and other organic sulfur compounds. On the bases of the reported reaction pathway of sulfur containing compounds with AMF [19], the reaction was suggested as shown in Figure S6 in supplementary file. Job's method of continuous variation was used to know the reaction molar ratio. It was 1:1 (drug: reagent) product taking into consideration that AMF has 2 Hg atoms and requires 2 sulfur moieties to chelate with them. This can be explained by the fact that QTF is fumaric acid salt which is a diprotic acid where 2 moles of quetiapine combine with 1 mole of fumaric acid. The data from this investigation are presented in Figure S7 in supplementary file.

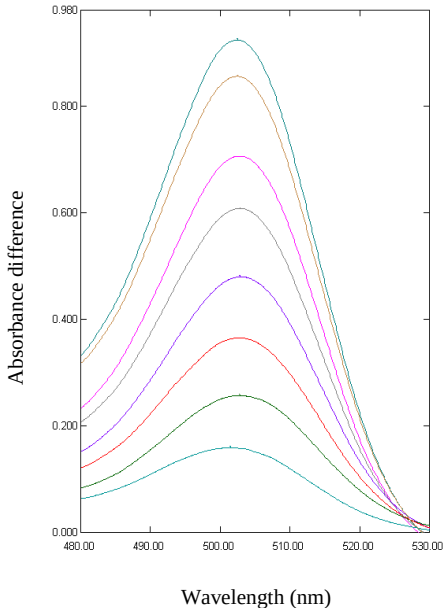

Figure 3: Absorption spectra of the reaction product of 30, 20, 30, 40, 50, 60, 70, 90 and 100 µg/mL QTF with AMF in methanol.

3.2. Reaction conditions optimization

The laboratory factors for production of the measured color products were examined to get the optimum conditions which assure the best results for QTF assay. Each factor was changed while others constant. The optimum conditions are shown in (Table 1). The concentration effect of the reagent was examined (0.005 M $KMnO_4$, 0.0023 M ceric ammonium sulfate and 1×10^{-4} M AMF). According to the obtained data, 3 mL $KMnO_4$ was enough to produce the highest color intensity. However, any increase in $KMnO_4$ volume above 3 mL would not increase in the absorbance reading (Figure S8 in supplementary file). On the other hand, methods II and III depend on measurement of absorbance decrease of the reagents, and it was found that maximum absorbance of 1.5 was achieved using 1.3 mL and 2.3 mL of ceric ammonium sulfate and AMF respectively; therefore, these volumes were chosen. In method I; NaOH solution (0.50 M) was utilized as alkaline medium source. Different volumes of NaOH solution were used to prepare the reaction mixtures.

Then, the color product's absorbance was monitored. It was noticed that color intensity increased along the increasing of NaOH solution volume. However, the absorbance was decreased when NaOH solution volume exceeded 2 mL. Figure S9 in supplementary file demonstrates the effect of NaOH on the generated color product. In method II, H_2SO_4 (2 M) solution was utilized to provide an acidity medium. Different volumes of H_2SO_4 solution were used to prepare the reaction mixtures (0.25, 0.50 and 1.00 mL) then absorbance of ceric reagent with and without addition of the drug were recorded. Increasing volume of H_2SO_4 solution produced increase in the suppressive effect of the drug on ceric absorbance. However, the absorbance was decreased when H_2SO_4 solution volume exceeded 0.5 mL. Figure S10 in supplementary file demonstrates the effect of H_2SO_4 concentration on absorbance difference upon addition of QTF to ceric. For method I, previous studies for oxidation with alkaline permanganate endorse reaction at room temperature due to poor reproducibility obtained upon application of elevated temperatures [20-24]. Consequently, the effect of temperature on the measured signal was studied only in methods II and III. In method II, heat was required in QTF reaction with ceric required. Effect of heating temperature on the oxidation of QTF by ceric was studied by performing the reaction in a thermostatically controlled water bath at varying temperatures (50-100°C). It was found that by increasing the temperature, the suppressive effect of the drug on ceric absorbance increased until it reached maximum at 90°C which was chosen as optimum reaction temperature (Figure S11 in supplementary file). On the other hand, for method III, increasing temperature did not show any improvement in measurement, accordingly, the reaction was performed at room temperature. The reaction condition with respect to time was optimized to achieve optimum sensitivity by monitoring the color development in method I at room temperature (25±5°C), where solutions were allowed to stand for 70 min and the signal was measured every 10 min. It was observed that the maximum absorbance was obtained at 50 min above which no further increase in absorbance. For method II, solutions were heated at 90°C for 70 min and the difference in absorbance was measured every 10 min. It was observed that the maximum sensitivity of measurement was achieved at 50 min. For method III, solutions were allowed to stand at room temperature (25±5°C) for 20 min and the signal was measured every 5 min. It was found that the drug reacts instantaneously with AMF, therefore, absorbance measurements were carried out at zero time. The effect of time on absorbance of the formed color products is illustrated in Figure S12 in supplementary file. Water was considered an ideal solvent for the oxidation reactions of QTF with $KMnO_4$ (method I) and ceric ammonium sulfate (method II). On the other hand, reaction with AMF (method III) was carried out in different solvents such as methanol, acetonitrile and water (Figure S13 in supplementary file). Methanol was found to be an ideal solvent for the reaction with AMF due to the maximum absorbance difference attained. This observation is a clear evidence for the greenness of the proposed methods. The optimized experimental conditions for the three methods are summarized in Table S1 in supplementary file.

3.3. Validation of the proposed methods

International Conference on Harmonization (ICH) validation guidelines of analytical procedures (Q2R1) [25] were followed for the validation of the suggested methods. Series of different concentrations of QTF were used to evaluate the linearity of the proposed methods. The least-squares treatment of the absorbance data versus the corresponding concentrations (n = 6, 5 and 7 for methods I, II and III respectively) was used to generate the linear regression equations. The obtained absorbance readings were directly proportional to corresponding concentrations of QTF. All obtained data was presented in Table 1. Regression analysis for the calibration curves of the three proposed methods showed good linear relationship over the concentration ranges of 5-35, 1-6 and 30-100 µg/mL for methods I ($KMnO_4$), II (Ceric) and III (AMF), respectively. The correlation coefficients for the proposed methods were greater than 0.9995 (r = 0.99957, 0.99987 and 0.99961) with RSD% of slope values (S_b%) less than 2% (1.47, 0.93 and 1.24%) for methods I, II and III respectively. The limit of detection (LOD) and the limit of quantitation (LOQ) were calculated according to the ICH guidelines. The LOD values were 1.11, 0.12 and 2.68 µg/mL, LOQ values were 3.35, 0.37 and 8.13 µg/mL while molar absorptivity (ε) values were 30838, 184124 and 9776 for methods I, II and III respectively. Therefore, method II was proved as the most sensitive method

among all suggested methods. The accuracy and within-day precision for the suggested methods were tested at three different concentrations of QTF within the studied. All data are shown in Table 2. The obtained RSD % and E_r % values were accepted. Therefore, the suggested methods were proved to be accurate and precise. the influence of small variations in experimental conditions were evaluated to examine the robustness of the proposed methods. These experimental conditions included volume of base (NaOH) for method I, volume of acid (H_2SO_4) and temperature for method II, concentration of reagents, reaction times and wavelengths on the performance of the proposed methods. In these experiments, all parameters were kept constant except one parameter was changed. The recovery was calculated each time. None of these variables significantly influenced the proposed methods. The recoveries ranged from 99.40 to 101.30% with SD values ranging from 0.21 to 1.85 (Table 3). In addition, the relative standard deviations were less than 1.85, 1.75, 1.23 for method I, II and III respectively. This provided an indication of reliability and robustness during routine application of the proposed methods in the analysis of QTF. Stock standard solutions of QTF were stable for 2 weeks when stored refrigerated at 4 ºC. Moreover, the absorbance readings of obtained color solutions were stable for one hour at room temperature.

3.4. Assay of QTF in its tablets

The proposed methods were applied to QTF analysis in Quitapex® and Seroquel® tablets. External standard method was used for recoveries estimation. The analysis data were summarized in Table 4. The obtained data proved good accuracy and precision. The obtained recoveries data were good and that proved that no interference from any of the tablet excipients. Also, these data were compared statistically with those of the reported method [26] using ANOVA test. The obtained F-value was below the critical value. Therefore, there were no significant differences in the suggested methods compared with the reported one. The obtained data proved that the suggested methods can be applied to QTF analysis in its tablets.

3.5.Comparison with reported spectrophotometric methods

There are several spectrophotometric methods for QTF assay [2-17]. A comparison of the three suggested methods with these reported methods was presented in Table S2. It was precisely clear for method II (reaction with ceric) which provided the highest sensitivity among the three methods. Moreover, the suggested procedures offer more advantages of being easy, cheap and without extraction or tedious multi-step analytical method which most likely lead to loss of the analyte. Chemicals and solvents used were mild and eco-friendly compared to several previously reported methods which included the use of hazardous solvents such as chloroform and other chlorinated hydrocarbons. Furthermore, the proposed methods not required expensive instrumentation and/or complex analytical reagents.

4. Conclusion

This study presented green analytical methods for the analysis of quetiapine fumarate as a raw material and also in its pharmaceutical dosage forms. The suggested methods based on the use of the oxidation of the drug and the complexation of sulfur with mercury containing reagent. The proposed methods are comparable or even advantageous to the previously reported spectrophotometric methods [26] in several aspects such as greenness, simplicity, sensitivity of measurement, additionally; the data were taken in the visible region. The suggested methods were easy as there were no need for sample pretreatment and/or tedious extraction of the analyte. Moreover, the proposed methods utilized simple technique. These methods were validated and These methods were validated and successively applied for the analysis of the drug in its tablets with good accuracy and precision.

Table 1: Analytical parameters for the determination of QTF using the proposed spectrophotometric methods.

Parameter \ Reagent	KMnO4 (method I)	Ceric ammonium sulfate (method II)	AMF (method III)
Concentration range (µg/mL)	5 – 35	1 – 6	30 – 100
Apparent molar absorptivity (L mol^{-1} cm^{-1})	30838	184124	9776
Intercept (a)	0.0190	0.0393	0.0066
S_a	0.0117	0.0078	0.0090
Slope (b)	0.0349	0.2085	0.0110
S_b	0.0005	0.0019	0.0001
RSD% of the slope (S_b %)	1.49	0.91	1.27
Correlation coefficient (r)	0.99957	0.99987	0.99961
$S_{y/x}$	0.01361	0.0080	0.00816
F value	4607	11560	6415
Significant	2.82×10^{-7}	1.77×10^{-6}	5.74×10^{-9}
LOD (µg/mL)	1.11	0.12	2.68
LOQ (µg/mL)	3.35	0.37	8.13

Table 2: Precision and accuracy for the determination of (QTF) in bulk form using the proposed spectrophotometric methods.

		Nominal value (µg/mL)	Found ± SD [a] (µg/mL)	RSD(%)[b]	E_r(%)[c]
$KMnO_4$ (method I)	**Within-day**	**10**	10.10 ± 0.10	0.99	1.00
		20	20.29 ± 0.26	1.28	1.45
		30	30.06 ± 0.28	0.93	0.2
	Between-day	**10**	9.95 ± 0.19	1.90	-0.50
		20	20.01 ± 0.34	1.70	0.05
		30	29.88 ± 0.56	1.87	-0.40
Ceric ammonium sulfate (method II)	**Within-day**	**2**	2.02 ± 0.007	0.35	1.00
		4	3.99 ± 0.051	1.28	-0.25
		6	5.90 ± 0.015	0.25	-1.66
	Between-day	**2**	2.01 ± 0.039	1.94	0.50
		4	4.00 ± 0.053	1.32	0.00
		6	5.95 ± 0.047	0.79	-0.83
AMF (method III)	**Within-day**	**40**	39.94 ± 0.55	1.38	-0.15
		60	59.10 ± 0.08	0.14	-1.50
		90	90.39 ± 1.28	1.42	0.43
	Between-day	**40**	40.11± 0.71	1.77	0.28
		60	59.67 ± 1.02	1.71	-0.55
		90	90.54 ± 0.27	1.71	0.60

[a] Mean ± standard deviation for three determinations
[b] % Relative standard deviation
[c] % Relative error

Table 3: Robustness of the proposed methods for analysis of QTF by various reagents

	Parameter	Mean ± SD	RSD%
Method I	$KMnO_4$ volume ± 0.2 mL	99.51 ± 1.85	1.85
	NaOH volume ± 0.2 mL	99.40 ± 1.55	1.56
	Reaction time ± 5 min	99.51 ± 1.85	1.86
	Wavelength ± 2 nm	101.27 ± 0.32	0.31
Method II	Ceric volume ± 0.1 mL	100.60 ± 1.76	1.75
	Sulphuric acid volume ± 0.05 mL	100.51 ± 1.01	1.00
	Reaction time ± 5 min	100.09 ± 1.53	1.53
	Wavelength ± 2 nm	101.30 ± 0.21	0.21
Method III	AMF Volume ± 0.2 mL	99.94 ± 1.23	1.23
	Wavelength ± 2 nm	100.26 ± 1.07	1.07

Table 4: Application of the proposed spectrophotometric methods for the determination of QTF in Seroquel ® tablets and Quitapex® tablet.

Using external standard analysis (Seroquel® tablet)				
Method / Results	**$KMnO_4$ (method I)**	**Ceric ammonium sulfate (method II)**	**AMF (method III)**	**Reported method [26] ****
%Found ± SD *	100.29 ± 1.28	99.17 ± 1.94	98.98 ± 1.62	99.89 ± 1.34
RSD%	1.28	1.96	1.63	1.34
Variance (SD^2)	1.63	3.76	2.62	1.79
ANOVA (single factor)				
F / **F critical**				
1.991956 / **3.238872**				
(Quitapex® tablet)				
%Found ± SD *	99.10 ± 1.88	98.22 ± 1.02	100.55 ± 1.75	99. ± 1.40
RSD%	1.89	1.03	1.74	1.39
Variance (SD^2)	3.53	1.04	3.06	1.96
ANOVA (single factor)				
F / **F critical**				
2.96043 / **3.238872**				

*Mean ± standard deviation for five determinations.
** Reported A_{max} spectrophotometric method.

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