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TITRIMETRIC AND SENSITIVE SPECTRO-PHOTOMETRIC METHODS FOR THE ASSAY OF QUETIAPINE FUMARATE IN PHARMACEUTICAL FORMULATIONS

Quetiapine fumarate (QTF) is a selective monoaminergic antagonist with high affinity for the serotonin Type 2 ($5HT_2$), and dopamine type 2 (D_2) receptors. Titrimetric and spectrophotometric assay of quetiapine fumarate (QTF) using perchloric acid and acetic acid as reagents are described. The first method (method A) is a non-aqueous titrimetric method and is based on the titration of QTF in glacial acetic acid with 0.01 M acetous perchloric acid using crystal violet as indicator. In the second method (method B), QTF has been measured in 0.1M acetic acid spectrophotometrically at a wavelength of 222 nm. The titrimetric method was applicable over the range of 2.0-20.0 mg of QTF. The reaction stoichiometry of 1:3 is obtained which served as the basis for calculation. In spectrophotometry, Beer's law was obeyed over the concentration range of 1.25-15.0 μg mL^{-1}. The linear regression equation of the calibration graph was A = 0.0115 + 0.0673c with a regression coefficient (r) of 0.9986 (n = 7). The apparent molar absorptivity was calculated to be 4.25×10^4 L $mol^{-1}cm^{-1}$ and the Sandell sensitivity was 0.0145 μg cm^{-2}. The limits of detection (LOD) and quantification (LOQ) calculated as per the ICH guidelines were 0.07 and 0.21 μg mL^{-1}, respectively. Accuracy and precision of the assays were determined by computing the intra-day and inter-day variations at three different levels of QTF. The intra-day and inter-day relative standard deviation (%RSD) were in the range of 0.99-2.88 and 1.65-2.32%, for method A and B, respectively, with an acceptable percentage relative error (%RE) < 2%. The methods were successfully applied to the determination of QTF in two different brands of tablets with good accuracy and precision and without detectable interference by excipients. The methods have demonstrated to be simple and easy to apply in routine usage and do not need any costly instrumentation. Therefore, the proposed procedures are advantageous and can be adopted in routine quality control laboratories in the developing or under developed countries.

Key words: quetiapine fumarate; assay; non-aqueous titrimetry; UV-spectrophotometry; pharmaceuticals.

Quetiapine fumarate (QTF) is an atypical antipsychotic drug [1], synthesized originally by Warawa and Migler in 1988 [2] and can be used alone or in combination with other medications to treat schizophrenia and bipolar disorder [3,4]. The chemical name of QTF is 2-(2-(4-dibenzo[b,f] [1,4]thiazepine-11-yl-1--piperazinyl)ethoxy)ethanol, fumaric acid (1:2 salt) (Figure 1) with formula $C_{29}H_{33}N_3O_{10}S$ and molecular weight of 615.66.

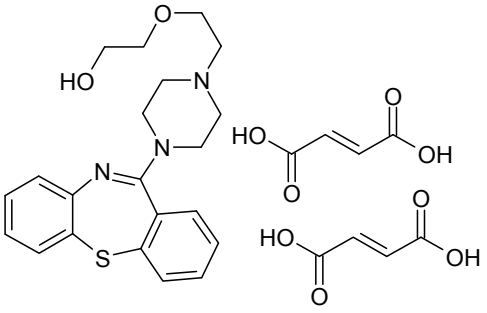

Figure 1. Chemical structure of QTF.

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Many methods have been used to determine QTF in biological samples or matrices and these include HPLC with UV [5-11], chemiluminescence [12], electrospray ionization MS [13-16], tandem MS/MS detection [17-18], UPLC with tandem MS detection [19,20], GC [21] and voltammetry [22]. QTF is not official in any pharmacopoeia. Methods based on different techniques such as polarography [23], capillary zone electrophoresis [24,25], HPTLC [26,27], HPLC [28-30] and UV spectrophotometry [24,31] have earlier been employed for the determination of QTF in pharmaceutical formulations.

There is no titrimetric method reported for the determination of QTF in pharmaceuticals. Pucci *et al.* [24] have reported a spectrophotometric method for the determination of QTF after converting the drug into its free base by using 50 mM phosphate buffer (pH 2.5) as solvent. The assay was carried out by measuring the absorbance of quetiapine free base at a wavelength of 246 nm. The linearity was observed in the range of 5-25 μg mL^{-1} QTF. The UV spectrophotometric method developed by Fursule *et al.* [31] involved the measurement of QTF at 290 nm in water and Beer's law was obeyed in the range 6-54 μg mL^{-1}. The reported spectrophotometric methods have some disadvantages such as usage of organic toxic solvent such as methanol or buffer [24] and less sensitivity [31]. In the present paper, micro-titrimetric and sensitive spectrophotometric procedures are described for the assay of QTF in pharmaceuticals.

EXPERIMENTAL

Apparatus

Perkin-Elmer Lambda-35 UV-Vis double beam spectrophotometer, Elico UV/Vis SI-164 spectrophotometer, Shimadzu Pharmaspec 1700 UV/Vis spectrophotometer and Systronic UV-Vis spectrophotometer 2201, all with 1 cm matched cells were used for absorbance measurements. Two Borosil and two Qualigens burettes were used for titration. Chromatographic analysis was carried out using an Alliance Waters HPLC system equipped with Alliances 2657 series low pressure quaternary pump, a programmable variable wavelength UV-Vis detector, Waters 2996 photodiode array detector and auto sampler. Data were collected and processed using Waters Empower 2.0 software.

Materials

All chemicals used were of analytical reagent grade. QTF pure drug was kindly provided by Cipla Ltd, Bangalore, India, as a gift and used as received. Qutipin-200 (Batch No. AD82847; EXP 1/12/2011) and Qutipin-100 (Batch No. AD90376; EXP 1/1/2012) tablets-manufactured from Sun Pharmaceuticals Ltd, Mumbai, India, were purchased from local market.

Reagents and solutions

All solutions were made in glacial acetic acid (S. D. Fine Chem, Mumbai, India) in method A unless mentioned otherwise.

Perchloric acid (0.01 M). A stock solution of 0.1 M perchloric acid was purchased from Merck, Mumbai, India, and it was diluted appropriately with glacial acetic acid to get a working concentration of 0.01 M and standardized with pure potassium hydrogen phthalate (S. D. Fine Chem, Mumbai, India) [32].

Crystal violet indicator (0.1%). Prepared by dissolving 50 mg of dye (S. D. Fine Chem, Mumbai, India) in 50 mL of glacial acetic acid.

Acetic acid (CH_3COOH) (0.1 M). Appropriate volume of glacial acetic acid was diluted with distilled water to get 0.1 M CH_3COOH for use in spectrophotometry.

Standard drug solution

A stock standard solution containing 2 mg mL^{-1} QTF was prepared in glacial acetic acid and used in titrimetry (method A). A stock standard solution equivalent to 250 μg mL^{-1} QTF was prepared by dissolving accurately weighed 25 mg of pure drug in 100 mL of 0.1M CH_3COOH. This solution was further diluted with the same solvent to get working concentration of 50 μg mL^{-1} for use in spectrophotometric work (method B).

General analytical procedures

Method A. An aliquot of the pure drug solution equivalent to 2.0-20.0 mg of QTF was measured accurately and transferred into a clean and dry 100 mL titration flask and the solution was diluted to 25 mL by adding glacial acetic acid. Two drops of crystal violet indicator were added and titrated with standard 0.01 M perchloric acid to a blue colour end point. The amount of the drug in the measured aliquot was calculated from:

$$\text{Amount (mg)} = VM_wR/3$$

where V – volume of perchloric acid required, mL; M_w – – relative molecular mass of the drug (615.66); and R – – molarity of the perchloric acid, obtained from standardization with potassium hydrogen phthalate (100% pure, primary standard) where the stoichiometric relationship between $HClO_4$ and PHP is 1:1.

Method B, calibration curve. Into a series of 10 mL calibration flasks, aliquots of QTF standard solu-

tion (50 μg mL^{-1}) equivalent to 1.25-15.0 μg mL^{-1} QTF were accurately transferred and the volume made up to mark with 0.1M CH_3COOH. The absorbance of each solution was measured at 222 nm *vs* 0.1 M CH_3COOH.

The calibration curve was plotted and the concentration of the unknown was read from the calibration graph or computed from the regression equation derived using Beer's law data.

Procedure for analysing QTF tablets

Method A. Twenty tablets from each brand (Qutipin-200 or Qutipin-100) were weighed separately and ground into a fine powder. An amount of powder equivalent to 200 mg of QTF was weighed accurately and transferred into a 100 mL calibrated flask, 70 mL of glacial acetic acid was added and shaken for about 20 min followed by warming for 10 min. Then the volume was made up to the mark with glacial acetic acid, mixed well and filtered using Whatman No. 42 filter paper. The first 10 mL portion of the filtrate was discarded. A suitable aliquot was next subjected to analysis following the procedure as described earlier.

Method B. An amount of powdered tablet equivalent to 25 mg of QTF from Qutipin-200 or Qutipin--100 was weighed and transferred into a 100 mL volumetric flask. The content was shaken well with about 70 mL of 0.1 M CH_3COOH for 20 min. The mixture was diluted to the mark with the same acid. It was filtered using Whatman No. 42 filter paper. The first 10 mL portion of the filtrate was discarded and a subsequent portion was diluted to get a working concentration of 50 μg mL^{-1} and subjected to analysis by spectrophotometry as described for pure drug.

Reference HPLC method

A quantity of tablet powder containing 25 mg QTF was dissolved ultrasonically and diluted to 50 mL with methanol. The solution was filtered through a 0.45 μm filter membrane and a 1 mL portion of the filtrate was diluted to 10 mL with methanol. A 10 μL portion of above solution was injected and analysed on a 5 μm Hypersil ODS-C18 column (25 cm×4.6 mm i.d.), with methanol/0.5% triethylamine (39:11, pH 7-8) as mobile phase at a flow rate of 1 mL/min and UV detection was made at 254 nm. Figure 2 is a typical chromatogram obtained for QTF under the described chromatographic conditions.

Recovery study

Method A. Three different amounts of pure drug solution equivalent to 4.0, 8.0 and 12.0 mg QTF were spiked into QTF tablet solution containing 7.95 mg (Qutipin-200) or 8.25 mg (Qutipin-100), mixed well and the resulted solution was subjected to analysis by following the general titrimetric procedure.

Method B. Different aliquots of pure drug solution equivalent to 2.0, 4.0 and 6.0 μg mL^{-1} QTF were spiked separately into tablet solutions containing 3.91 and 4.10 μg mL^{-1} QTF from Qutipin-200 and Qutipin--100, respectively, and then the analysis was performed as described in the procedure for calibration curve.

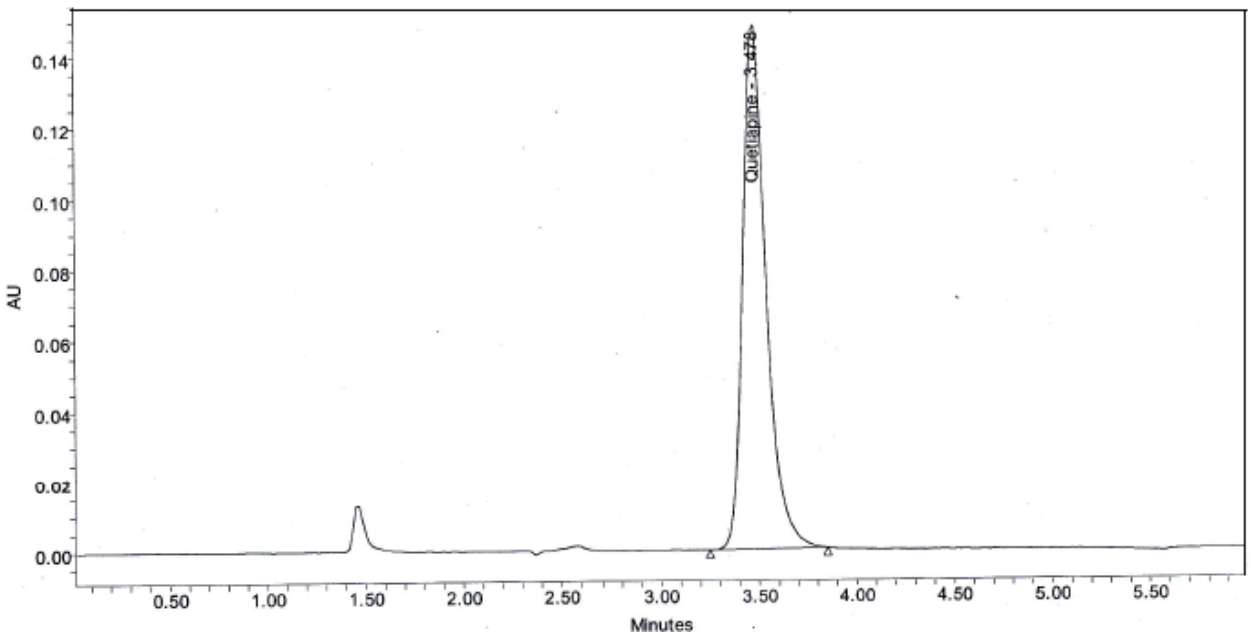


Figure 2. A typical chromatogram obtained for 50 μg mL^{-1} QTF (R_t = 3.48 min) under the experimental conditions described in reference method.

Validation

Intra-day and inter-day accuracy and precision. Three different amounts/concentrations of QTF within the range of study in each method (6.0, 12.0 and 18.0 mg, method A, and 4.0, 8.0 and 12.0 μg mL^{-1}, method B) were analyzed in seven replicates during the same day (intra-day precision) and five consecutive days (inter-day precision) by following general analytical procedures. For inter-day precision, each day analysis was performed in triplicate and pooled-standard deviation was calculated by using the following formula [33]:

$$S_p = \sqrt{\frac{(X_i - \overline{X}_1)^2 + (X_j - \overline{X}_2)^2 + (X_k - \overline{X}_3)^2}{N - k}}$$

where X_i, X_j and X_k are individual amount/concentration of QTF found in each set; X_1, X_2 and X_3 are the mean values found for the data sets 1, 2 and 3, respectively, and N is the total number of measurements from k sets.

The accuracy was evaluated as percentage relative error (*%RE*) between the found and taken amounts/concentrations using the relationship:

$$\%RE = \frac{(QTF_T - QTF_F)}{QTF_T} \times 100$$

where the subscripts T and F refer to taken and found, respectively.

Determination of limits of detection (*LOD*) and quantification (*LOQ*)

A replicate measurement of the absorbance of 0.1 M CH_3COOH at 222 nm was made (n = 5) and the standard deviation value was evaluated. The limits of detection (*LOD*) and quantification (*LOQ*) are calculated according to ICH guidelines [34] using the formulae:

$LOD = 3.3S/b$ and $LOQ = 10S/b$

where S is the standard deviation obtained from absorbance values measured for 0.1 M CH_3COOH, and b is the slope of the calibration plot.

Ruggedness

A triplicate analysis was performed by four different analysts, using four different burettes (method A) and four different spectrophotometers (method B) for three different amounts (6.0, 12.0 and 18.0 mg, method A) or concentrations (4.0, 8.0 and 12.0 μg mL^{-1}, method B) of QTF. The amount/concentration of QTF found in each case was calculated. The inter-mediate precision expressed as *RSD* was evaluated.

THEORY

Method A

The method is based on the principle that substances which are weakly basic in aqueous medium exhibit enhanced basicity in non-aqueous media thus allowing their easy determination. Acetic acid displays acidic properties in dissociating to produce protons [35]:

$$CH_3COOH \longleftrightarrow CH_3COO^- + H^+$$

But in the presence of perchloric acid, a far stronger acid, it will accept a proton:

$$CH_3COOH + HClO_4 \longleftrightarrow CH_3COOH_2^+ + ClO_4^-$$

$$2CH_3COOH_2^+ + 2CH_3COO^- \longleftrightarrow 4CH_3COOH$$

Since the $CH_3COOH_2^+$ readily donates its proton to a base, a solution of perchloric acid in glacial acetic acid functions as a strongly acidic solution. When a weak base, such as QTF, is dissolved in acetic acid, the acetic acid exerts its levelling effect and enhances the basic property of the QTF. It is possible, therefore, to titrate a solution of QTF in acetic acid with perchloric acid. The titration results revealed that a reaction stoichiometry of 1:3 (drug:titrant) was obtained which served as the basis for calculation. Using 0.01 M perchloric acid, 2.0-20.0 mg of QTF was conveniently determined. The relationship between the drug amount and the titration end point was examined. The linearity between two parameters is apparent from the correlation coefficient of 0.9985 obtained by the method of least squares. From this it is implied that the reaction between QTF and perchloric acid proceeds stoichiometrically in the ratio 1:3 in the range studied. The possible neutralization reaction is postulated in Scheme 1.

Method B

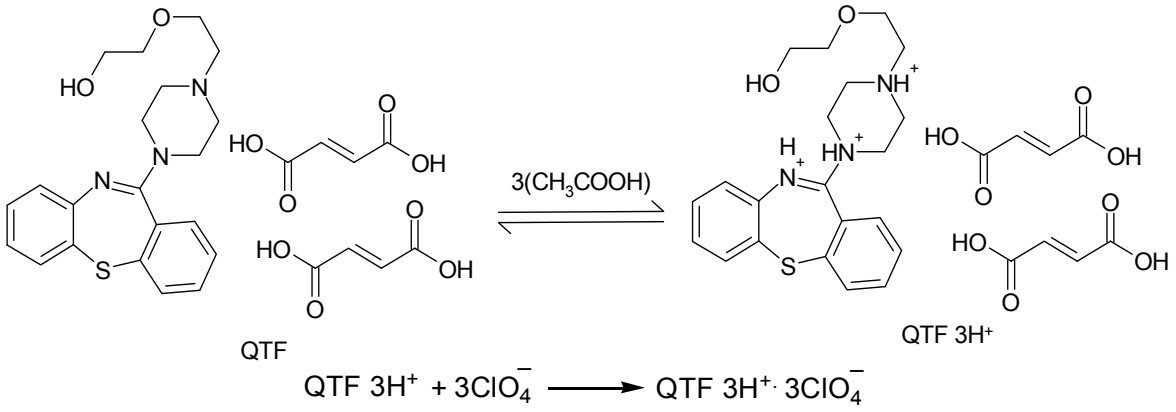
Spectral characteristics. A solution of QTF in 0.1 M CH_3COOH exhibited an absorption maximum at 222 nm. At this wavelength the corresponding blank solution had insignificant absorbance as shown by the absorption spectra in Figure 3.

RESULTS AND DISCUSSION

Validation of the proposed analytical procedures

Conformity to Beer's law (method B). Beer's law was obeyed for the concentration range of 1.25–15 μg mL^{-1} of the drug in 0.1 M CH_3COOH. The calibration graph was described by the regression equation:

$y = a + bx$



Scheme 1. Possible neutralization reaction between QTF and perchloric acid in glacial acetic acid medium.

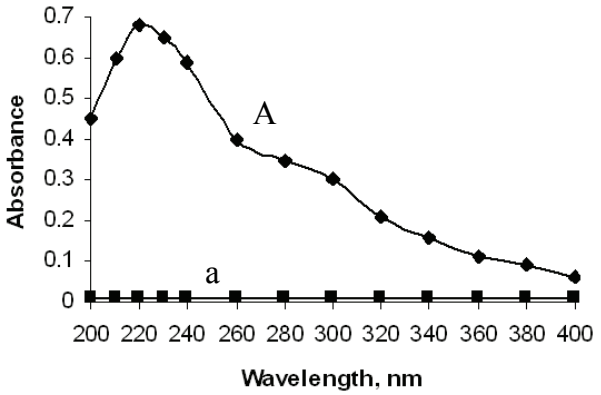


Figure 3. Absorption spectra of QTF (10 μg mL^{-1}) in 0.1 M CH_3COOH (A) and 0.1 M CH_3COOH (a).

where *y* – absorbance of 1-cm layer of solution; *a* – – intercept; *b* – slope; *x* – concentration in μg mL^{-1}). Regression analysis of the Beer's law data using the method of least squares was made to evaluate the slope (*b*), intercept (*a*) and correlation coefficient (*r*) for each system. A log-log plot of absorbance *vs.* concentration yielded a straight line with a slope equal to 0.9804, further establishing the linear relation between the two variables. The optical characteristics such as molar absorptivity and Sandell sensitivity (limit of determination as the weight in μg per mL of solution, which corresponds to an absorbance of *A* = = 0.001 measured in a cuvette of cross-sectional area 1 cm^2 and *l* = 1 cm path length) values [36] are recorded and found to be 4.25×10^4 L mol^{-1} cm^{-1} and 0.0145 μg cm^{-2}, respectively. The limits of detection (*LOD*) and quantitation (*LOQ*) are calculated to be 0.07 and 0.21 μg mL^{-1}, respectively. The high value of ε and low value of Sandell sensitivity and *LOD* indicate the high sensitivity of the proposed method.

Intra-day and inter-day accuracy and precision

The repeatability of the proposed methods was determined by performing replicate measurements for three different amounts/concentrations of QTF. The results of this study are compiled in Table 1 and speak of the excellent intermediate precision (*RSD* < 3%) and accuracy (*RE* < 2%) of the results.

Ruggedness of the methods

The ruggedness of the methods was evaluated on the basis of intermediate precision expressed as *RSD*. The inter-analysts RSD values were in the range from 0.99 to 2.01% whereas the inter-instruments *RSD* for the same QTF amounts/concentrations were 1.89-2.50% suggesting that the developed methods are rugged.

Analysis of pharmaceutical formulations

The proposed methods were applied for the quantification of QTF in commercial tablets. The results were compared with those obtained using a re-

Table. 1. Intra-day and inter-day accuracy and precision (RE - relative error; RSD - relative standard deviation)

Method A							Method B					
Amount of QTF taken mg	Intra-day accuracy and precision			Inter-day accuracy and precision			Concentration of QTF taken μg mL^{-1}	Intra-day accuracy and precision			Inter-day accuracy and precision		
	QTF found, mg	*%RE*	*%RSD*	QTF found, mg	*%RE*	*%RSD*		QTF found μg mL^{-1}	*%RE*	*%RSD*	QTF found μg mL^{-1}	*%RE*	*%RSD*
6.0	6.08	1.33	1.23	6.10	1.67	2.69	4.0	3.93	1.75	2.12	4.06	1.50	1.98
12.0	12.11	0.92	0.99	12.13	1.08	2.88	8.0	7.95	0.63	1.65	8.09	1.13	2.13
18.0	18.12	0.67	1.02	18.10	0.56	1.99	12.0	12.03	0.25	1.56	12.11	0.92	2.32

ference method [30]. The reference method is a liquid chromatography where QTF has been detected using UV detector at 254 nm. The assay was performed for two different brands as described in the chromatographic procedure and the percentage recovery of QTF was evaluated and it was found to be in the range 97.8–103.1. The statistical comparison of the results revealed (Table 2) no any significant difference between the performance of the proposed methods and reference method with respect to accuracy and precision as revealed by the Student's *t*-value and variance ratio *F*-value [37].

Recovery study

The accuracy of the proposed methods was further ascertained by performing recovery experiments by standard addition method. The recovery was assessed by determining the agreement between the measured standard concentration and added known concentration to the sample. The percentage recovery values obtained from three replicate measurements at each level of drug were in the range from 97.25 to 103.1 with relative standard deviation in the range 0.62–1.46. Closeness of the results to 100% showed good accuracy of the methods. The results are shown in Table 3.

CONCLUSIONS

One titrimetric and one spectrophotometric method were developed for the determination of quetiapine fumarate and the methods were validated as per the current ICH guidelines. The proposed methods have distinct advantages over the existing methods in terms of simplicity of technique and ease of performance and do not need expensive and highly sophisticated equipment or high-cost organic solvents which are required for HPLC. In particular, the titrimetry is much simpler in technique, more rapid than all the methods reported so far for QTF. It is applicable over a semi-micro range (2-20 mg), requires inexpensive chemicals, yet provides very accurate and precise results. The proposed spectrophotometric method is more sensitive ($\varepsilon = 4.25\times10^4$ L mol^{-1} cm^{-1}) than the reported methods [24,31] and fairly accurate and precise. Hence, the methods can be used in routine analysis in pharmaceutical quality control laboratories.

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Table 2. Results of analysis of tablets by the proposed methods and statistical comparison of the results with the reference method

Tablet brand name	Nominal amount, mg/tablet	Found[a] (percent of label claim±*SD*)		
		Reference method	Proposed methods	
			Method A	Method B
Qutipin-200	200	98.56±1.26	99.42±1.74	97.8±0.76
			t = 0.91	*t* = 1.19
			F = 1.91	*F* = 2.75
Qutipin-100	100	101.4±1.52	103.1±2.04	102.6±0.94
			t = 1.51	*t* = 1.54
			F = 1.80	*F* = 2.61

[a]Mean value of 5 determinations; tabulated *t*-value at the 95 % confidence level and for four degrees of freedom is 2.77; tabulated *F*-value at the 95 % confidence level and for four degrees of freedom is 6.39

Table 3. Results of recovery study via standard-addition method

Tablets studied	Titrimetry				Spectrophotometry			
	QTF in tablet, mg	Pure QTF added, mg	Total found mg	Pure QTF recovered±SD[a], %	QTF in tablet μg mL^{-1}	Pure QTF added μg mL^{-1}	Total found μg mL^{-1}	Pure QTF recovered±SD[a], %
Qutipin-200	7.95	4.0	12.00	101.3±0.62	3.91	2.0	5.86	97.32±0.86
	7.95	8.0	15.93	99.75±0.85	3.91	4.0	7.90	99.64±1.04
	7.95	12.0	20.06	100.9±0.62	3.91	6.0	9.93	100.3±0.92
Qutipin-100	8.25	4.0	12.14	97.25±1.46	4.10	2.0	6.16	103.1±0.62
	8.25	8.0	16.36	101.4±0.82	4.10	4.0	8.12	100.6±0.74
	8.25	12.0	20.35	100.8±1.14	4.10	6.0	10.18	101.3±0.87

[a]Mean value of three determinations

Commission, New Delhi, India, for awarding Meritorious Research Fellowship.

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NAUČNI RAD

VOLUMETRIJSKA I OSETLJIVA SPEKTROFOTOMETRIJSKA METODA ZA ODREĐIVANJE KUETIAPIN FUMARATA U FARMACEUTSKIM PREPARATIMA

Kuetiapin fumarat (KTF) je selektivni monoaminoergični antagonist sa visokim afinitetom prema receptorima serotoninu Tip 2 ($5HT_2$), i dopaminu tip 2 (D2). U radu su opisana volumetrijsko i spektrofotometrijsko određivanje kuetiapin fumarata (KTF) koristeći perhlornu i sirćetnu kiselinu, kao reagense. Prvi metod (metoda A) je nevodena volumerijska metoda i zasniva se na titraciji KTF u glacijalnoj sirćetnoj kiselini sa 0,01 M perhlornom kiselinom koristeći kristal violet kao indikator. U drugoj metodi (metoda B), KTF je određivan u 0,1 M sirćetnoj kiselini spektrofotometrijski na talasnoj dužini od 222 nm. Volumetrijska metoda je primenjiva u opsegu od 2,0-20,0 mg KTF. Stehiometrijiski odnos od 1:3 je poslužio kao osnova za dalje računanje. U spektrofotometriji, Beer-ov zakon je važio u opsegu koncentracija od 1,25-15,0 mg ml^{-1}. Linearna regresija jednačine kalibracione krive je A = 0,0115 + 0,0673c sa koeficijentom regresije 0.9986 (n = 7). Prividna molarna apsorpcija je određena i iznosi $4,25\times10^4$ L $mol^{-1}cm^{-1}$, a Sandell-ova osetljivost je 0,0145 mg cm^{-2}. Granice detekcije (LOD) i kvantifikaciju (LOK) su računate po ICH upustvu i iznose 0,07 i 0,21 mg ml^{-1}, respektivno. Tačnost i preciznost testova određene su korišćenjem dnevnih i višednevnih varijacija na tri različita nivoa KTF. Relativne standardne devijacije dnevnih i višednevnih varijacija bile su u opsegu od 0,99--2,88 i 1,65-2,32% za metode A i B, respektivno, uz prihvatljivu relativnu grešku (<2 %). Metode su uspešno primenjene u određivanju KTF u dve različite vrste tableta sa dobrom tačnošću i preciznošću. Metode su se pokazale jednostavnim i lakim za primenu u svakodnevnoj upotrebi bez korišćenja skupih instrumenata. Ove procedure imaju prednosti i mogu biti usvojene u laboratorijama za rutinsku kontrolu kvaliteta u zemljama u razvoju ili nerazvijenim zemljama.

Ključne reči: kuetiapin fumarat; test; nevodena titracija; UV spektrofotometrija; farmaceutski.