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Validated HPLC and Thin Layer-Densitometric Methods for Determination of Quetiapine Fumarate in Presence of its Related Compounds

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Abstract

Two chromatographic methods were developed for determination of quetiapine fumarate in presence of three related compounds; namely quetiapine N-oxide, des-ethanol quetiapine and quetiapine lactam, in pure form and pharmaceutical preparation. The first method depended on densitometric thin layer chromatography where the separation was achieved using silica gel $60F_{(254)}$ plates as stationary phase and toluene:1,4-dioxane:dimethylamine (5:8:2, v/v/v) as a mobile phase. The second method utilized the reverse phase high performance liquid chromatographic technique, using C18 column and methanol: acetonitrile: phosphate buffer (pH 5.3) in a ratio (19:40:41, v/v/v) as a mobile phase. The flow rate was1 mL min^{-1} and UV-detection was at wavelength 220 nm. The validation parameters of the developed methods were calculated and the results obtained were statistically compared with those of the HPLC manufacturer method.

Keywords: HPLC; Quetiapine fumarate related compounds; Thin layer-densitometry

Introduction

Quetiapine Fumarate (QTF) is a psychotropic agent belonging to a chemical class of dibenzothiazepine derivatives. The chemical designation is 2-(2-(4-dibenzo (b,f)(1,4)thiazepin-11-yl-1-piperazinyl) ethoxy)-ethanol fumarate (2:1) (salt). It is present in tablets as the fumarate salt. It is a white or almost white powder, moderately soluble in water and soluble in methanol and 0.1N HCl. It is used to treat psychosis associated with parkinson's disease and chronic schizophrenia [1], synthesized originally by Warawa and Migler [2] and can be used alone or in combination with other medications to treat schizophrenia and bipolar disorder [3,4]. Several methods have been reported for the determination of QTF in bulk powder, pharmaceutical preparations and biological samples. These included UV-Visible spectrophotometric methods [5-9], HPTLC methods [10-12], capillary zone electrophoretic method [13], voltammetry [14] and HPLC methods [15-17].

The evaluation of QTF related compounds has been an important issue that was recommended by regulatory agencies. Few papers were published for estimation of QTF in presence of its related compounds including; a GC method for determination of QTF in presence of 2-(2-chloroethoxy)ethanol and n-methyl-2-pyrrolidinon [18] and four HPLC methods, where it was determined in presence of piperazine (PI), quetiapine lactam (QL) and dibenzothiazepine piperazinyl ethanol hemifumarate compounds in the first method [19], and in presence of two related compounds quetiapine N-oxide (QO) and (QL) in the second one [20], also in presence of (QL),(PI) and Des-ethanol quetiapine (DQ) in the third one with long run time (18 mins) [21] , finally with (PI), (DQ) and quetiapine dimer using binary gradient mode in the fourth one [22]. And a RP-UPLC method for determination of QTF in presence of (QO), (PI), (DQ), S-oxide and quetiapine dimer using complicated binary gradient elution with linearity range (62.5-187.5 µg mL^{-1}) [23]. No method of the mentioned HPLC methods determined QTF in presence of this combination of related compounds; QO, DQ and QL in a simple isocratic isocratic elution mode for the mobile phase with good resolution between the four proposed components compared.

So far to our knowledge, only one stability-indicating HPTLC method for the determination of QTF in presence of its degradation products has been reported [24] but no TLC-densitometric method was reported for the determination of QTF in the presence of its related compounds.

The aim of our work was to develop more sensitive HPLC method with higher throughput using a mobile phase in a simple isocratic mode of elution and also to develop a selective, accurate, reproducible HPTLC-densitometric method which has the advantage of being of low cost and a faster technique when compared to HPLC method for determination of QTF in presence of the three related compounds; QO, DQ and QL (Figure 1) in raw material and in dosage form.

Materials and Methods

Instruments

Camag TLC scanner (Camag, Muttenz, Switzerland) operated with winCATS software version 3.15, Linomat IV autosampler (Camag, Muttenz, Switzerland). 100-µL Camag microsyringe (Hamilton, Bonaduz, Switzerland), Precoated silica gel aluminium Plates 60 F254 (20 cm × 20 cm) 250 µm thicknesses (E. Merck, Darmstadt, Germany).

Agilent 1200 series chromatographic system equipped with quaternary pump, microvacuum degasser, thermostatic column compartment and variable wavelength UV–VIS detector was used. Sample injections were made through an Agilent 1200 series

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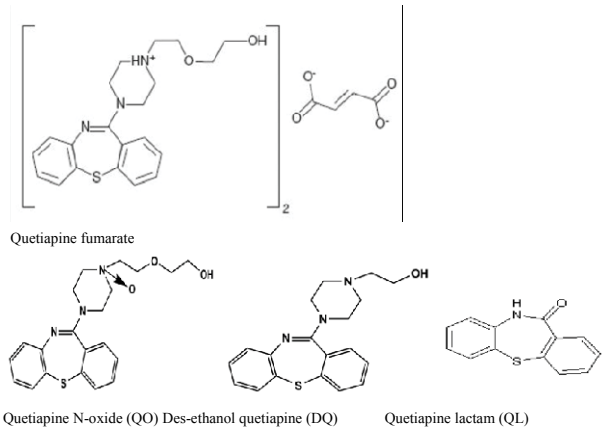

Figure 1: Structures of quetiapine fumarate and its related compounds.

autosampler. Data collection and processing were performed using Agilent ChemStation software, version A.10.01. Column SN (USUXB06014) Agilent-C_{18} column (150 mm × 4.6 mm, 5 µm particle size i.d.) was from (Agilent Technologies, Polo Alto, CA, USA).

pH-meter (Jenway3505, UK), equipped with combined glass electrode was used for pH adjustment.

Ultrasound sonicator (Crest Ultrasonics, New York).

Chemicals and solvents

All chemicals used throughout the work were of analytical grade and solvents were of HPLC grade; Acetonitrile, methanol and orthophosphoric acid (Riedel-dehaen, Sigma-Aldrich, Germany), potassium dihydrogen orthophosphate and dimethyamine (ADWIC, Egypt), toluene (Euromedex, France), 1,4-dioxane (Alpha Chemika, India).

Samples

Quetiapine fumarate, (99.4%) and its related compounds, (99.8%) were kindly supplied by National Organization of Drug Control and Research (NODCAR) institute, Cairo, Egypt.

Seroquel® tablets were manufactured by Astra Zeneca, Egypt. Each tablet was labeled to contain 25 mg of quetiapine fumarate.

Chromatographic conditions

HPTLC-densitometry: The mobile phase was selected as mixture of toluene, 1,4-dioxane and dimethylamine in a ratio of (5:8:2, v/v/v). The densitometric scanning was performed at 225 nm. Analysis was performed on precoated 20 × 20 cm silica gel 60 F_{254} aluminium sheets (E. Merck, Darmstadt, Germany). Samples were applied to the plates using Camag Linomat IV applicator along with 100 µL Camag microsyringe. Spots were applied 1.5 cm apart from each other and 2 cm from the bottom edge. The chromatographic chamber was pre-saturated with the mobile phase for 15 min and the developing distance on TLC-plate was 180 mm.

HPLC: The mobile phase used was mixture of methanol, acetonitrile and phosphate buffer (pH adjusted to 5.3 using orthophosphoric acid) in a ratio of (19:40:41, v/v/v). The mobile phase was freshly prepared and filtered by vacuum filtration through 0.45 µm filter and degassed by ultrasound sonicator for 50 minutes just prior to use. The analysis was done under isocratic condition at a flow rate 1 mL min^{-1} and at room temperature using UV detector at 220 nm.

Standard solutions

Stock standard solutions (1.0 mg mL^{-1}) each of QTF, QO, DQ and QL were prepared in methanol. The working standard solution (0.1 mg mL^{-1}) of each one was prepared by further dilution of each stock solution with methanol.

Construction of calibration curve

HPTLC-densitometry: The linearity was evaluated by analyzing a series of different concentrations of the drug in the range of 1.0-11.0 µg $spot^{-1}$. Each concentration was repeated three times, in order to provide information on the variation in peak areas values among samples of the same concentration. The plates were developed using the specified mobile phase. The spots were scanned at 225 nm. The average peak area was calculated for each concentration of QTF and was plotted versus their concentration to obtain the calibration graph and the regression equation was then computed.

HPLC: Aliquots (0.1-3.0 mL) from QTF standard working solution were transferred into a series of 10 mL volumetric flasks and then diluted with methanol to obtain a concentration range of (1.0-30.0 µg mL^{-1}). Twenty microliters were injected for each concentration in triplicate and chromatographed using the HPLC conditions described above. The average peak area was calculated for each concentration of QTF and was plotted versus their concentration to obtain the calibration graph and the regression equation was then computed.

Assay of laboratory prepared mixtures

Solutions containing different ratios of QTF, QO, DQ and QL were prepared from their respective working standard solutions and diluted with methanol. The average peak areas of the laboratory prepared mixtures were calculated and processed as described above for the two proposed methods. The concentration of QTF was calculated using the computed regression equations.

Application to pharmaceutical preparation (Seroquel® tablet)

Seroquel® tablet was individually weighed to get the average weight of the tablet. A sample of the powdered tablets, claimed to contain 100.0 mg of drug was transferred separately to 100 mL volumetric flask, sonicated for 20 minutes with 50 mL methanol, then the volume was brought to 100 mL with the same solvent and filtered to prepare stock solution, having a concentration of (1.0 mg mL^{-1}). A working standard solution (0.1 mg mL^{-1}) was prepared by further dilution of the stock solution with methanol.

In HPTLC-densitometric method, aliquot of 5.0 mL was transferred from the prepared stock solution into 10 mL volumetric flask, completed to the volume with methanol. Then, 10 µL were applied onto HPTLC plates (n=5). While, in HPLC method, aliquot of 1.0 mL was transferred from the prepared working solution into10-mL volumetric flask and the volume was completed with methanol. Then, 20 µL from this dilution were injected (n=5).

The general procedure described above for each method was followed. Then, the concentration of QTF in its pharmaceutical preparation was calculated.

Application of standard addition technique

To check the validity of the proposed chromatographic methods, standard addition technique was applied by adding known amounts of the pure drug to the previously analyzed tablets. In HPTLC-

densitometry, three aliquots (5.0 mL) of the previously prepared stock solution of tablet (1.0 mg mL^{-1}) were mixed with aliquots (1.0, 1.5, 2.0 mL) of pure stock standard solution of QTF, separately 10 mL volumetric flasks and the volume was completed with methanol. Then, 10 µL from each dilution were applied onto HPTLC plates in triplicate. In HPLC method, three aliquots (1.0 mL) of the working standard solution of tablet (0.1 mg mL^{-1}) were mixed with aliquots (0.5, 1.0, 1.5 mL) of pure working standard solution of QTF, separately into 10 mL volumetric flasks and the volume was completed with methanol. Then, 20 µL from each final dilution were injected in triplicate.

The general procedure described above for each method was followed and the concentration of the added pure QTF standard was calculated from the specified regression equation.

Results and Discussion

Development of analytical methods for the determination of pharmaceuticals in the presence of related compounds without previous chemical separation is always a matter of interest. The aim of this work was to establish sensitive, accurate and precise HPTLC-densitometric and HPLC methods for determination of QTF in presence of its related compounds namely; quetiapine N-oxide (QO), des-ethanol quetiapine (DQ) and lactam (QL), in its bulk powder and commercial tablets.

Related compounds of quetiapine fumarate

Seven potential impurities, including by-products, starting materials and intermediates were identified in pharmaceutical substance QTF and characterized by spectroscopic methods (MS, IR, and NMR) [25].

During the stability studies of QTF in the laboratory, several batches have been analyzed for purity by HPLC. QO (oxidation product) at level 0.1% was detected by ion-pair reversed-phase high performance liquid chromatography (HPLC) [26]. As per the stringent regulatory requirements recommended by ICH the impurities ≥0.1% must be identified and characterized and determined [27].

DQ is a byproduct in the process of QTF preparation, Based on the spectral data, the impurity was characterized as2-(4-dibenzo(b,f)(1,4) thiazepine-11-yl-1-piperazinyl)1-2-ethanol [28].

According to the Scheme (Warawa and Migler) for synthesis of QTF; QL is considered the starting material [28].

Method optimization

HPTLC-densitometry: The proposed HPTLC-densitometric method is based on the difference between the R_f values of QTF and its three related compounds due to the difference in their polarities and their migration rates on TLC plates. The chromatographic conditions were optimized by spotting the drug with its related compounds on TLC plates and developing in different solvent systems to achieve best separation. Different solvent systems were tried. Initially a system of toluene and methanol in a ratio of (8:2, v/v) was tried, but only the drug moved from the baseline as the three related compounds were highly polar. So, a mixture of toluene, dioxane and dimethylamine was tried in different ratios to obtain a good separation between QTF and its related compounds. The optimum mobile phase used was toluene:1,4-dioxane:dimethylamine in a ratio of (5:8:2, v/v/v). The chromatographic system described in this work allowed complete separation of QTF from its related compounds, as shown in Figure 2. Calibration graph was obtained by plotting the average peak area against the concentration of QTF. Linearity range was found to be 1.0–11.0 µg $spot^{-1}$ using the following regression equation:

A= 684.53 C – 278.13 r=0.9997

Where A represents the average peak area, C is the concentration in µg $spot^{-1}$ and r is the correlation coefficient.

HPLC: The chromatographic conditions, especially the composition of mobile phase, were optimized to achieve a good resolution and symmetric peak shapes for the drug and its related compounds, as well as a short analytical time. Initially a mixture of methanol, acetonitrile and phosphate buffer (pH adjusted to 6.4) in a ratio of (20:50:30, v/v/v) was used as a mobile. The peaks of QTF and QL were overlapped. Increasing the ratio of buffer to (20:40:40, v/v/v) resulted in increasing the retention time of QTF and QL peaks to more than 10 minutes and there was still some overlapping between QTF and QL peaks. By decreasing pH to 5.3, the separation between QTF and QL overlapped peaks was resolved. The optimum mobile phase used for the simultaneous determination of QTF and its related compounds was a mixture of methanol, acetonitrile and phosphate buffer (pH adjusted to 5.3) in a ratio of (19:40:41, v/v/v). The average retention time (R_t)± SD, for 6 replicate injections for QTF, QO, DQ and QL were found to be 3.61 ± 0.04, 2.53 ± 0.01, 3.20 ± 0.02 and 4.24 ± 0.04; respectively. A typical chromatogram of bank injection and QTF and its related compounds are shown in Figures 3 and 4, respectively.

Calibration graph was obtained by plotting the average peak area against concentration of QTF (µg mL^{-1}). Linearity range was found to be 1.0-30.0 µg mL^{-1} using the following regression equation:

A =68.611 C - 2.2421 r=0.9998

Where A represents the average peak area, C is the concentration in µg mL^{-1} and r is the correlation coefficient.

Method validation

International conference on Harmonization (ICH) guidelines [29] for method validation was followed for validation of the suggested methods.

Linearity: The linearity of the proposed methods for determination of QTF was evaluated by analyzing a series of different concentrations of the drug in the range of 1.0-11.0 µg $spot^{-1}$ for HPTLC-densitometric method and 1.0-30.0 µg mL^{-1} for HPLC method. Each concentration was repeated three times, in order to provide information on the variation in peak areas values among samples of the same concentration. Linear relationships were obtained by plotting the drug concentrations against the average peak area obtained for each concentration of QTF. The validation parameters for the regression equation of the adopted

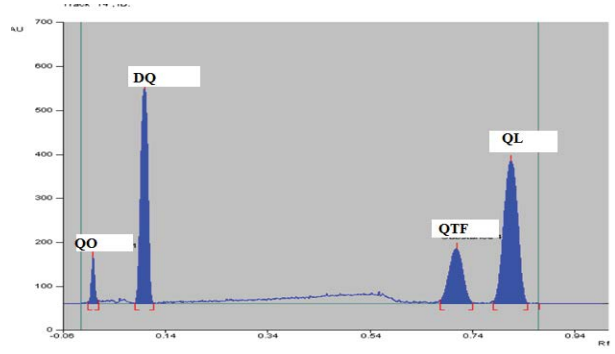

Figure 2: HPTLC chromatogram of QO, DQ, QTF and QL mixture of concentration (10.0 µg $spot^{-1}$) each, using toluene:dioxane:dimethylamine (5:8:2, by volume) at 225 nm.

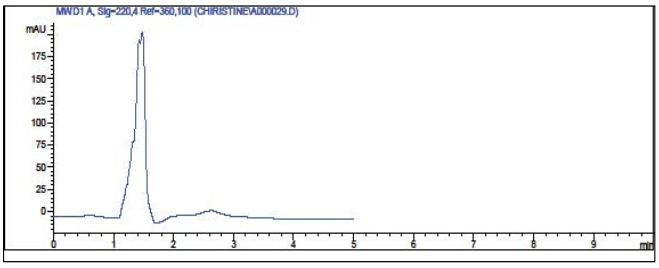

Figure 3: Chromatogram of blank injection.

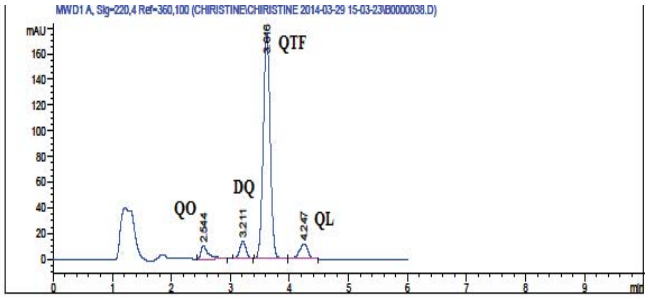

Figure 4: HPLC Chromatogram of QO (10 µg mL^{-1}), DQ (10 µg mL^{-1}), QTF (20 µg mL^{-1}) and QL (10.0 µg mL^{-1}) mixture, using methanol:acetonitrile:phosphate buffer (pH=5.3) (19:40:41, v/v/v) at 220 nm.

chromatographic methods are given in Table 1.

Accuracy: The accuracy of the proposed method was checked by the analysis of five different concentrations of authentic samples in triplicate. The concentrations of QTF were calculated using the regression equation for each of the two proposed chromatographic methods and then the mean percentage recovery and the relative standard deviation (RSD%) were calculated, as shown in Table 1 indicating the satisfactory accuracy of the proposed methods.

Precision: Three replicates of each concentration were analyzed on the same day to determine the intra-day precision of the methods. To confirm the inter-day precision, three replicates of each concentration were analyzed at three separate days using the developed chromatographic methods and calculating RSD%. Results in Table 1 indicate satisfactory precision of the proposed methods.

Detection and quantitation limits: According to (ICH) recommendation [29] the limits of detection (LOD) and limits of quantitation (LOQ) were determined using the formula: LOD or LOQ=k SD/slope of the response, where k=3.3 for LOD and 10 for LOQ and SD is the residual standard deviation of the regression line and results are presented in Table 1.

Specificity: The specificity of a method is the extent to which it can be used for analysis of a particular analyte in a mixture or matrix without interference from other components. The specificity of the proposed methods was tested by the analysis of six laboratory prepared mixtures containing different ratios of QTF and its three related compounds; QO, DQ and QL. The laboratory prepared mixtures were analyzed according to the previous procedures described under each of the proposed methods. The specificity was assessed to show that QTF could be measured without interference from its related compounds. Well resolved peaks for QTF from its related compounds indicated that there was no interference observed at the retention times of the drug. Satisfactory results were obtained (Table 2) indicating the high specificity of the proposed methods.

System suitability: System suitability test parameters must be checked to ensure that the system was working correctly during the analysis. Method performance data including capacity factor, selectivity, resolution, and tailing factor are listed in Table 3. All data was satisfactory and indicative of the good specificity of the method for determination of QTF in presence of its related compounds.

Robustness: The robustness of the chromatographic methods was investigated by the analysis of samples under a variety of experimental conditions such as small changes in TLC mobile phase ratio; toluene:dioxane:dimethylamine (6:8:2 and 5:9:2, v/v/v) and deliberate variations in HPLC mobile phase pH (5.5 and 5.6). Results presented in Table 4, indicate that the capacity of the utilized methods remain unaffected by these small deliberate variations, providing an indication for the reliability of the proposed chromatographic methods during routine work.

Analysis of pharmaceutical preparation

The proposed methods were applied for the determination of QTF in Seroquel® tablets, Figures 5 and 6. The results, shown in Table 5, are satisfactory and with good agreement with the labeled amount.

Standard addition technique

The interference of excipients in the pharmaceutical formulations was studied using standard addition method. The mean percentage recoveries and the standard deviation were calculated (Table 5). According to the obtained results a good accuracy and precision was observed. Consequently, the excipients in pharmaceutical formulations did not interfere in the analysis of QTF in its pharmaceutical formulation.

Statistical analysis

The results obtained by applying the proposed chromatographic methods were statistically compared to the reference HPLC method used for QTF analysis. The calculated t and F values were less than the theoretical ones indicating that there was no significant difference between the proposed and the manufacturer method with respect to accuracy and precision, as presented in Table 6.

Validation parameters		HPTLC-densitometry	HPLC
Linearity range		1.0-11.0 µg spot^{-1}	1.0-30.0 µg ml^{-1}
Correlation coefficient (r)		0.9997	0.9998
Slope		684.53	68.61
Intercept		-278.13	-2.24
LOD		0.29 µg spot^{-1}	0.20 µg ml^{-1}
LOQ		0.90 µg spot^{-1}	0.56 µg ml^{-1}
Accuracy (Recovery% ± RSD)		100.36 ± 1.41	100.21 ± 0.41
Precision (RSD%, n=9)	Intra-day	1.65	0.36
	Inter-day	1.93	1.93

Table 1: Characteristic parameters for the regression equations of the proposed methods, for determination of QTF.

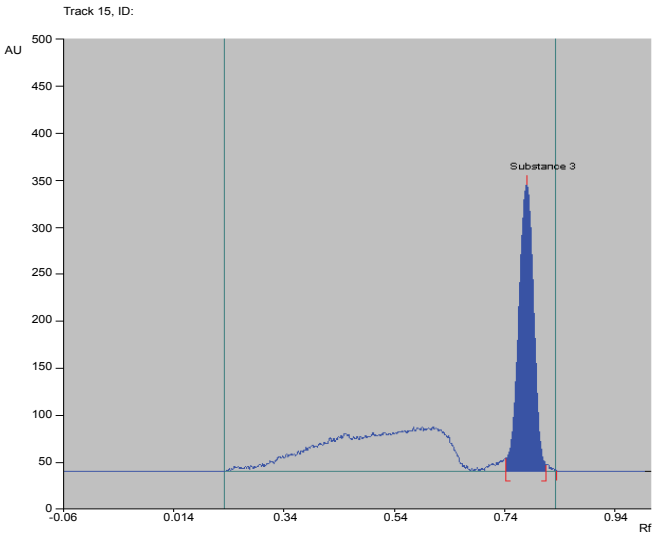

Figure 5: HPTLC chromatogram of QTF in Seroquel® tablets.

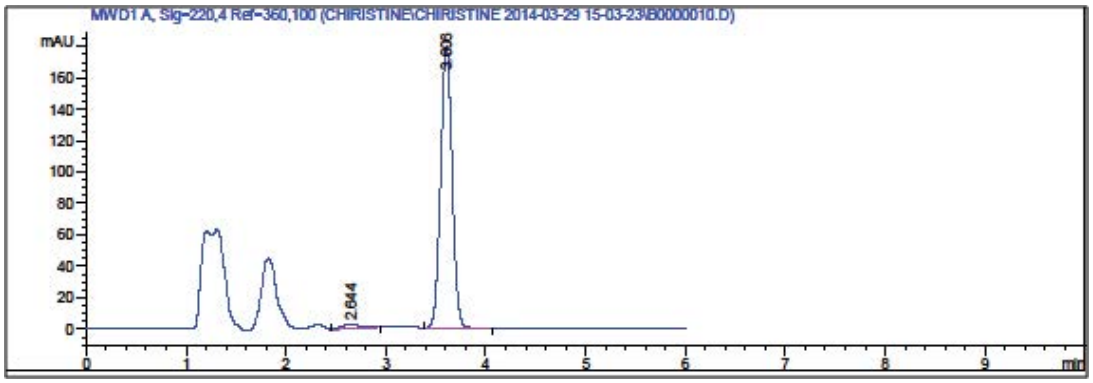

Figure 6: HPLC Chromatogram of QTF in Seroquel® tablets.

Ratio(QTF:QO:DQ:QL)	HPTLC (%Recovery[a] of QTF)	HPLC (%Recovery[a] of QTF)
10:0.01:0.01:0.01	99.76	100.16
10:0.02:0.02:0.02	99.34	100.18
10:0.03:0.03:0.03	101.20	101.22
10:0.06:0.06:0.06	100.65	100.17
10:0.1:0.1:0.1	101.12	100.79
10:0.2:0.2:0.2	101.75	101.15
Mean % ± SD	100.63 ± 0.91	100.61 ± 0.50

[a]Average of three determinations.

Table 2: Results obtained for the analysis of laboratory prepared mixtures containing different ratios of the intact QTF with its related compounds, by the proposed chromatographic methods.

Parameters	HPTLC-densitometry				HPLC				Reference values
	QO	DQ	QTF	QL	QO	DQ	QTF	QL	
t_R, min (HPLC)/R_f (HPTLC)	0.01	0.08	0.70	0.81	2.53	3.20	3.61	4.24	
Tailing factor (T)	0.90	0.76	0.93	1.02	0.73	0.96	1.01	1.18	T≤ 2
Plates number (N)					3040	4608	4688	3991	N>2000
Height equivalent to theoretical plate (HETP; cm plate^{-1})					0.049	0.032	0.031	0.037	The smaller the value, the higher the column efficiency
Resolution (R_s)	16	10.47	-	1.6	2.37	2.03	-	2.64	$R_s \geq 2$

Table 3: System suitability test results of the developed chromatographic methods for determination of QTF.

Parameters	HPTLC		HPLC	
	6:8:2, v/v/v	5:9:2, v/v/v	pH=5.5	pH=5.6
R_f (HPTLC) / t_R,min (HPLC) of QTF	1.015	0.97	3.56	3.58
T	0.97	1.04	1.02	1.07
N			4753	4634
R_s [b]	1.37	1.24	2.00	1.96

Table 4: Results [a] of robustness testing of the proposed chromatographic methods for determination of QTF.

Preparation	Claimed		%Recovery [a] ± SD		Standard addition technique			
					HPTLC		HPLC	
	HPTLC µg spot^{-1}	HPLC µg ml^{-1}	HPTLC	HPLC	Pure added µg spot^{-1}	%Recovery [b]	Pure added µg ml^{-1}	%Recovery [b]
Seroquel® tablets labeled to contain 25.0mg QTF	5.0	10.0	99.16 ± 1.27	100.67 ± 0.16	1.0	100.43	5.0	100.21
					1.5	99.52	10.0	100.35
					2.0	100.82	15.0	100.63
					Mean	100.27	**Mean**	100.39
					± SD	0.68	**± SD**	0.21

[a] Average of five determinations.
[b] Average of three determinations
Table 5: Quantitative determination of QTF in the pharmaceutical preparation and application of standard addition technique, using the proposed chromatographic methods.

Items	HPTLC- densitometry	HPLC	HPLC method [a]
Mean	99.16	100.67	99.21
RSD	1.17	0.16	0.97
variance	1.36	0.025	0.94
n	5	5	5
Student's t-test (2.44)	2.36	1.05	-
F-test (6.338)	2.45	1.18	-

The values between parenthesis are the theoretical values of t- and F-at P=0.05.
[a] HPLC method supplied by Astra Zeneca Company through personal communication using, the stationary phase; C18 column and mobile phase; methanol: acetonitrile: 0.02M dibasic ammonium phosphate (54:7:39, v/v/v) , UV detection at 254 nm and retention time 6mins.

Table 6: Statistical comparison between the results obtained, by applying the proposed methods and the manufacturer method for determination of QTF in pharmaceutical preparation.

Conclusion

The quality of pharmaceutical products is of vital importance for patient safety. The presence of related compounds or impurities may affect the efficacy and safety of pharmaceuticals. In this work, sensitive, accurate, precise and reproducible HPTLC-densitometric and HPLC methods were developed for the determination of QTF in the presence of three related compounds (QO, DQ and QL) which may be present in the pharmaceutical products in bulk powder and pharmaceutical preparation. The HPTLC-densitometric method has the advantage of being of low cost and is a faster technique when compared to HPLC. The proposed HPLC method offers high sensitivity, short run time and the use of isocratic elution mode for the mobile phase with good resolution between the four proposed components compared with the reported HPLC methods. Thus both methods can be used for routine analysis and quality control labs.

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