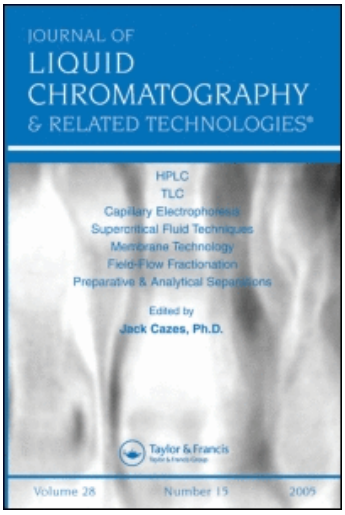

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Stability-Indicating HPLC Method for the Determination of Quetiapine: Application to Tablets and Human Plasma

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Stability-Indicating HPLC Method for the Determination of Quetiapine: Application to Tablets and Human Plasma

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Abstract: A stability-indicating reversed-phase high performance liquid chromatographic method was developed for the analysis of the antipsychotic drug quetiapine. Quetiapine was determined in presence of two of its degradation products; quetiapine N-oxide and quetiapine lactam. The analysis was carried out using a 250 mm × 4.6 mm i.d., 5 μm particle size Zorbax SB-Phenyl column. Mobile phase containing a mixture of acetonitrile and 0.02 M phosphate buffer (50:50) at pH = 5.5 was pumped at a flow rate of 1 mL/min with UV detection at 254 nm. The method showed good linearity in the range of 0.08–20 μg/mL with limit of detection (S/N = 3) 0.03 μg/mL (3.3×10^{-8} M). The suggested method was successfully applied for the analysis of quetiapine in bulk, tablets, and human plasma with average recoveries of 99.96 ± 1.25%, 101.37 ± 0.481%, and 100.82 ± 1.53%, respectively. The proposed method was also applied for the determination of quetiapine in the presence of some co-administered drugs as clomipramine, carbamazepine, and fluconazole.

Keywords: Stability-indicating, HPLC, Quetiapine, Degradation, Tablets, Human plasma

INTRODUCTION

Quetiapine (Ia) is one of the most recent "atypical" antipsychotic drugs.[1] Quetiapine fumarate is a dibenzothiazepine derivative. It is used in the treatment of schizophrenia and of mania associated with bipolar

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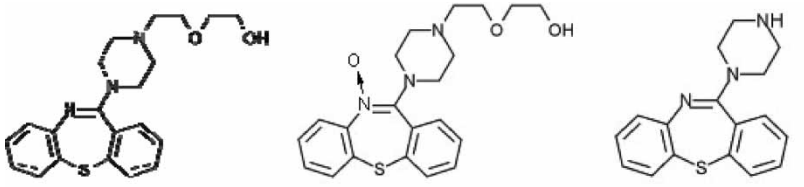
disorders.[2,3] It is reported to have affinity for serotonin, histamine, and adrenergic receptors, as well as dopamine D_2 receptors.



(Ia) quetiapine (Ib) quetiapine N-oxide (Ic) quetiapine lactam.

Reviewing the literature revealed that only three methods; spectrophotometric,[4] capillary zone electophoretic,[4] and voltammetric,[5] were used for the determination of quetiapine in tablets. Several methods have been reported for the quantitative determination of quetiapine in biological samples. These methods include gas chromatography,[6] HPLC with UV detection for the determination of quetiapine either alone,[7] in presence of other antipsychotics,[8,9] antidepressants,[8,10] and its metabolites.[11,12] Also, HPLC-electrospray ionization mass spectrometry,[13] ultra performance liquid chromatography tandem mass spectrometry,[14] HPLC-MS/MS method,[15] and capillary zone electrophoresis.[16]

In the present work, a HPLC method with UV detection was used for the analysis of quetiapine in the presence of two of its degradation products; quetiapine N-oxide (Ib) and quetiapine lactam (Ic). This method can be applied for the quality control of quetiapine tablets, as well as for the quantitative determination of quetiapine in human plasma.

EXPERIMENTAL

Apparatus

Chromatographic analyses were carried out using a Merck Hitachi Chromatograph model L-7100 equipped with a Rheodyne injector valve with a 20 μl loop, a L-7400 UV detector. The chromatograms were recorded using a Merck Hitachi D-7500 integrator. Mobile phase was filtered using millipore filter Sibata and degassed using Merck solvent L-7612 degasser.

Materials and Reagents

All reagents used are HPLC grade. Quetiapine and its degradation products (quetiapine N-oxide and quetiapine lactam) were kindly provided by Astra Zeneca (Macclesfield, UK). Temocapril was kindly provided by Sankyo

(Tokyo, Japan, through Drug Control Center, Riyadh, Saudi Arabia) as internal standard. Orthophosphoric acid 85% was from Riedel-deHäen, Sleeze, Germany. Acetonitrile and methanol from Sigma-Aldrich, Germany, sodium hydroxide from Winlab, UK, diethyl ether from Laboratory Rasayan, Sd. Fine Chemicals Ltd, Mumbai, India. Seroquel® tablets were kindly supplied by Astra Zeneca (Macclesfield, UK). Human plasma was kindly provided by MUH (Mansoura University Hospitals, Mansoura, Egypt) and kept frozen until used after gentle thawing. Blood samples were obtained from a healthy volunteer (male, 25 years old).

Chromatographic Conditions

Column: Zorbax SB-Phenyl column (250 mm × 4.6 mm i.d., 5 μm particle size), Agilent Technologies, USA. Mobile Phase: A solution containing a mixture of acetonitrile and 0.02 M phosphate buffer (50:50) at pH = 5.5, was prepared by 0.02 M orthophosphoric acid and adjusted to the pH using 0.02 M NaOH. The Flow rate was 1 mL/min, detector wave length: 254 nm. Internal standard: Temocapril (a 0.04 mg/mL stock solution was prepared in methanol).

Procedure for Preparation of Solutions

Stock solutions of 0.4 mg/mL of each of quetiapine fumarate, quetiapine N-oxide and quetiapine lactam degradation products were prepared in methanol. Working solutions were prepared by diluting the stock solutions with the mobile phase.

Procedure for Preparation of Calibration Curves

Working solutions containing 0.08–20.0 μg/mL of quetiapine were prepared by serial dilutions of aliquots of the stock solution together with an aliquot of internal standard solution containing 40.0 μg/mL of temocapril. Aliquots of 20 μL were injected (triplicate) and eluted with the mobile phase under the reported chromatographic conditions. The average peak area ratio between the internal standard and quetiapine versus the concentration of quetiapine in μg/mL was plotted. Alternatively, the corresponding regression equation was derived.

Procedure for Analysis of Bulk Substance

The method mentioned above was applied to the determination of the purity of quetiapine raw material. The percentage recoveries were calculated by referring to the calibration graph previously prepared or by applying the regression equation.

Procedure for Analysis of Dosage Forms

Ten tablets were accurately weighed, finely pulverized, and thoroughly mixed. An amount of pulverized tablets corresponding to 300 mg of the declared active principle (calculated as quetiapine free base) was weighed and transferred into a beaker. Methanol (80 mL) were added and the mixture was sonicated for 30 min. in an ultrasonic bath and then filtered, if necessary, into a 100 mL volumetric flask and completed to the volume with methanol. Aliquots of these solutions together with the internal standard were successively diluted with the mobile phase and then we proceeded as per section above. The nominal content of the tablets was obtained either from the calibration graph or from the regression equation.

Procedure for Analysis of Spiked Human Plasma

Suitable aliquots of quetiapine stock solution containing 0.08–2.00 μg/mL were transferred into centrifugation tubes. Human plasma (0.5 mL) was added to each tube. Then, alkalinization was achieved by the addition of 0.1 mL of NaOH (0.1 M) and the tubes were shaken for 1 min. Five milliliters of ether were added to each tube. After vortex mixing for 5 min., the mixtures were centrifuged at 3000 rpm for 6 min. at room temperature. Of the upper layer, 4 mL were carefully aspirated and the remainder was extracted once again with other 5 mL ether. Of the upper layer, 4 mL were collected together with the former. The ether was evaporated at room temperature. The residue was reconstituted using a minimal volume of methanol, sonicated for 10 min., then transferred into 10 mL volumetric flasks and diluted to the mark with the mobile phase. The resulting solutions were filtered using Millipore filters. Aliquots of 20 μL were injected (triplicate) and eluted with the mobile phase under the reported chromatographic conditions. The average peak area was plotted versus the concentration of quetiapine in μg/mL.

Procedure for Analysis of Patient Samples

A healthy volunteer (male, 25 years old) had been administered one 300 mg Seroquel® tablet after 8 hours of fasting. A blood sample was taken in the morning before taking the tablet as a blank. Then, blood samples were collected after several time intervals; 30 min, 1 hr, 1.5 hr, 2 hrs, 2.5 hrs, 3 hrs, and 4 hrs after administration. The samples were drawn into test tubes containing sodium citrate as anticoagulant and centrifuged at 1500 rpm for 15 min. The supernatant plasma was transferred into test tubes and the procedure described above was followed for the monitoring of the drug concentration in plasma.

RESULTS AND DISCUSSION

The proposed method permits the separation of quetiapine from two of its degradation products. It also permits the quantitation of quetiapine in commercial tablets and in human plasma. Figure 1 shows a chromatogram indicating good resolution of quetiapine ($t_R = 4.1$ min), temocapril ($t_R = 5.5$ min), quetiapine lactam ($t_R = 6.9$ min), and quetiapine N-oxide ($t_R = 8.5$ min). The proposed method offers high sensitivity as about 0.03 μg/mL of quetiapine could be detected accurately.

Chromatographic Performance

A well-defined symmetrical peak was obtained upon measuring the response of eluent under the optimized conditions after thorough experimental trials, that could be summarized as follows:

Choice of Column

Two different columns were used for performance investigations, including: Nucleosil 100-5 C18 column (150 mm × 4.6 mm i.d., 5 μm particle size),

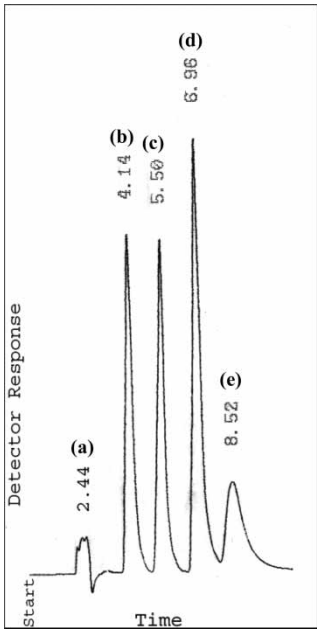


Figure 1. A chromatogram showing quetiapine with its degradation products: (a) solvent front, (b) 10 μg/mL quetiapine, (c) 40 μg/mL temocapril, (d) 10 μg/mL quetiapine lactam, (e) 10 μg/mL quetiapine N-oxide.

Macherey-Nagel, USA; Zorbax SB-Phenyl column (250 mm × 4.6 mm i.d., 5 μm particle size), Agilent Technologies, USA. The experimental studies revealed that the second column was more suitable since it produced nice peaks with high resolution and a very good sensitivity.

Choice of Appropriate Wavelength

The UV detector response of quetiapine was studied and the best wavelength was found to be 254 nm showing the highest sensitivity.

Choice of Internal Standard

Different drugs were investigated for the choice of a suitable internal standard. These drugs include; citalopram, diazepam, clopidogrel, mebeverine hydrochloride, diclofenac sodium, diflunisal, amiodarone HCl, clotrimazole, flupentioxol, nicardipine, resperidone, amikacin, and temocapril.

Temocapril was the best internal standard producing a well resolved peak from each of the drugs and the degradation products.

Mobile Phase Composition

Several modifications in the mobile phase composition were performed in order to study the possibilities of changing the selectivity of the chromatographic system. These modifications included the change of the type and ratio of the organic modifier, the pH, the strength of the phosphate buffer, and the flow rate. The results obtained are shown in Tables 1 to 4 respectively.

Type of Organic Modifier

Acetonitrile was replaced by methanol but it did not give good resolved peaks. Acetonitrile was the organic modifier of choice giving nice elegant highly sensitive peaks.

Table 1a. Effect of ratio of organic modifier on the capacity factor and the relative retention

	Capacity factor (K′)			Relative retention (α)		
Ratio (A/B)[a]	Quetiapine (Q)	Lactam (L)	N-oxide (N)	L/Q	N/Q	N/L
60/40	0.90	1.47	2.93	1.63	3.25	1.99
55/45	1.02	1.87	3.10	1.83	3.04	1.66
50/50	1.56	2.38	3.67	1.52	2.35	1.54
45/55	1.68	3.34	4.34	1.99	2.58	1.30
40/60	2.85	5.16	6.10	1.81	2.14	1.18

[a]A: acetonitrile; B: phosphate buffer.

Table 1b. Effect of ratio of organic modifier on the number of theoretical plates and resolution

	Number of theoretical plates (N)			Resolution (R)		
Ratio (A/B)	Quetiapine	Lactam	N-oxide	L/Q	N/Q	N/L
60/40	8212	6155	2183	3.83	8.18	5.88
55/45	2260	4579	2328	6.22	8.32	4.67
50/50	6454	11285	3020	6.00	8.44	4.89
45/55	7233	10677	2585	9.60	8.97	3.11
40/60	5659	10022	3325	10.60	8.95	2.42

Table 2a. Effect of pH on the capacity factor and the relative retention

	Capacity factor (K′)			Relative retention (α)		
Ph of the medium	Quetiapine	Lactam	N-oxide	L/Q	N/Q	N/L
5.0	0.38	0.98	1.55	2.58	4.08	1.58
5.5	0.61	1.44	2.42	2.36	3.97	1.68
6.0	0.47	0.88	2.39	1.87	5.08	2.71
6.5	1.61	1.91	3.48	1.19	2.16	1.82

Table 2b. Effect of pH on the number of theoretical plates and resolution

	Number of theoretical plates (N)			Resolution (R)		
pH of the medium	Quetiapine	Lactam	N-oxide	L/Q	N/Q	N/L
5.0	5187	7482	19789	5.40	8.03	3.36
5.5	6106	9772	3051	6.88	10.63	5.00
6.0	5497	8953	2384	8.70	16.44	13.00
6.5	4220	9222	2265	4.00	10.23	10.00

Table 3a. Effect of ionic strength of phosphate buffer on the capacity factor and the relative retention

	Capacity factor (K′)			Relative retention (α)		
Ionic strength	Quetiapine	Lactam	N-oxide	L/Q	N/Q	N/L
0.0075 M	0.97	1.70	3.01	1.75	3.11	1.77
0.01 M	0.75	1.71	2.76	2.28	3.68	1.61
0.02 M	0.84	1.77	2.93	2.11	3.49	1.65
0.03 M	0.69	1.75	2.69	2.54	3.89	1.54
0.04 M	0.65	1.70	2.57	2.61	3.95	1.51
0.05 M	0.68	1.59	2.70	2.34	3.97	1.69

Table 3b. Effect of ionic strength of phosphate buffer on the number of theoretical plates and resolution

	Number of theoretical plates (N)			Resolution (R)		
Ionic strength	Quetiapine	Lactam	N-oxide	L/Q	N/Q	N/L
0.0075 M	8600	7179	2233	5.84	9.09	5.26
0.01 M	7061	17003	2042	7.88	8.65	4.50
0.02 M	7666	17373	2188	6.27	8.06	4.48
0.03 M	2982	7832	2598	7.20	8.63	4.08
0.04 M	6292	7502	2397	8.18	8.69	3.70
0.05 M	2829	15153	1932	7.36	8.16	4.48

Table 4a. Effect of flow rate on the capacity factor and the relative retention

Flow rate (mL/min)	Capacity factor (K′)			Relative retention (α)		
	Quetiapine	Lactam	N-oxide	L/Q	N/Q	N/L
0.5	0.83	1.71	2.82	2.06	3.40	1.65
0.8	0.83	1.70	2.80	2.05	3.37	1.65
1.0	0.83	1.70	2.80	2.05	3.37	1.65
1.2	0.83	1.70	2.79	2.05	3.36	1.64
1.5	0.82	1.70	2.77	2.07	3.38	1.63

Table 4b. Effect of flow rate on the number of theoretical plates and resolution

Flow rate (mL/min)	Number of theoretical plates (N)			Resolution (R)		
	Quetiapine	Lactam	N-oxide	L/Q	N/Q	N/L
0.5	5119	7749	2822	6.58	8.86	4.70
0.8	5393	6613	3285	6.37	8.43	4.35
1.0	5381	11723	2723	6.47	8.04	4.27
1.2	5393	11722	2553	5.92	7.81	4.28
1.5	3462	7584	2360	6.00	8.87	4.17

Ratio of Organic Modifier

The effect of changing the ratio of organic modifier on the selectivity and retention times of the test solutes was investigated using mobile phases containing concentrations of 40–60% for acetonitrile. Table 1 shows that 50% acetonitrile was the best, giving well resolved peaks and the highest number of theoretical plates.

Ratios less than 40% resulted in complete overlap between the peaks of quetiapine lactam and quetiapine N-oxide, whereas ratios higher than 60% gave a complete overlap of quetiapine, temocapril, and lactam.

pH

The effect of changing the pH of the mobile phase on the selectivity and retention times of the test solutes was investigated using mobile phases of pH ranging from 5.0–6.5. Table 2 shows that pH of 5.5 was most appropriate giving well resolved peaks and the highest number of theoretical plates.

pHs less than 5.0 resulted in complete overlap between the peaks of quetiapine lactam and quetiapine N-oxide, whereas pHs higher than 6.5 produced complete overlap of quetiapine, temocapril, and lactam.

Ionic Strength of Buffer

The effect of changing the ionic strength of phosphate buffer on the selectivity and retention times of the test solutes was investigated using mobile phases containing a concentration of 0.0075–0.05 M of phosphate buffer. Table 3 shows that 0.02 M phosphate buffer was found to be the most suitable giving best resolution and the highest number of theoretical plates.

Flow Rate

The effect of flow rate on the formation and separation of peaks of the studied compounds was studied and a flow rate of 1 mL/min was optimal for good separation in a reasonable time (Table 4).

Validation of the Method

Concentration Ranges and Calibration Graphs

Under the above described experimental conditions, a linear relationship was established by plotting quetiapine concentrations against peak area ratio for quetiapine to the internal standard. The concentration range was found to be 0.08–20 μg/mL. Linear regression analysis of the data gave the following equation:

$$P = -0.001 + 0.093 \quad C(r = 0.9999)$$

where: C is the concentration of quetiapine in μg/mL and P is the peak area ratio.

The high value of the correlation coefficient (*r*- values > 0.999) with small intercept indicate the good linearity of the calibration graph. Statistical

analysis of the data gave small values of the standard deviation of the residuals, ($S_{y/x}$) 1.73×10^{-3}, of slope, (S_b) 7.96×10^{-5}, and of intercept, (S_a) 9.51×10^{-4} and the % relative error, (%Er) 0.39%.[17]

Limit of Quantitation (LOQ) and Limit of Detection (LOD)

The limit of quantitation (LOQ) was determined by establishing the lowest concentration that can be measured according to ICH Q2B recommendations,[18] below which the calibration graph is non linear and was found to be 0.08 μg/mL.

The limit of detection (LOD) was determined by establishing the minimum level at which the analyte can be reliably detected (S/N = 3) and it was found to be 0.03 μg/mL (3.3×10^{-8} M).

Accuracy and Precision

The proposed method was evaluated by studying the accuracy as percent relative error (%Er) and precision as percent relative standard deviation (%RSD) using three preparations with suitable concentrations as shown in

Table 5. Accuracy and precision data for quetiapine using the proposed method

	Quetiapine concentration, μg/mL		
Parameter	0.5	1.0	5.0
Intra-day[a]			
%Recovery	100.97	101.39	99.95
	100.44	100.80	100.56
	99.98	100.65	100.65
Mean ($\bar{x}$)	100.46	100.96	100.39
±S.D.	0.49	0.37	0.38
%R.S.D.	0.49	0.37	0.38
%Er.	0.28	0.21	0.22
Inter-day[b]			
%Recovery	100.97	101.30	99.95
	100.20	100.02	100.32
	99.90	101.26	100.47
Mean ($\bar{x}$)	100.36	100.89	100.25
±S.D.	0.55	0.76	0.27
%R.S.D.	0.55	0.75	0.27
%Er.	0.32	0.43	0.15

N.B. Each result is the average of three separate determinations.
[a]Intra-day: within the day.
[b]Inter-day: consecutive days.

Table 6. Assay of quetiapine in pure samples using the proposed and reference methods

	Quetiapine	
Parameters	Proposed	Ref. [4]
%Recovery	96.99	103.27
	99.17	99.06
	100.99	98.86
	100.97	100.07
	100.47	99.74
	101.39	100.29
	99.96	
	99.54	
	100.13	
	100.04	
Mean (x^-)	99.97	100.22
$\pm$S.D.	1.25	1.59
Variance	1.56	2.53
Students *t*-value	0.35	
Variance ratio *F*-value	1.62	

Tabulated *t*- and *F*-values at $p = 0.05$ are: 1.761 and 3.482, respectively [23].

Table 5. The intra-day (n = 3) and interday (n = 3) accuracy calculated as %Er was found to be within 0.21–0.28% and 0.15–0.43% for quetiapine, respectively. The repeatability of the assay was found to be within 0.37–0.49 (n = 3) at 0.5, 1.0, and 5.0 μg/mL. The reproducibility of

Table 7. Assay of quetiapine in Seroquel tablets using the proposed and reference methods

	Quetiapine (300 mg/mL)	
Parameters	proposed	Ref. [4]
%Recovery	101.92	101.41
	101.13	101.45
	101.05	100.69
Mean (x^-)	101.37	101.18
$\pm$S.D.	0.481	0.428
Variance	0.231	0.183
Students *t*-value	0.511	
Variance ratio *F*-value	1.262	

Tabulated *t*- and *F*-values at $p = 0.05$ are 2.132 and 19.000, respectively.

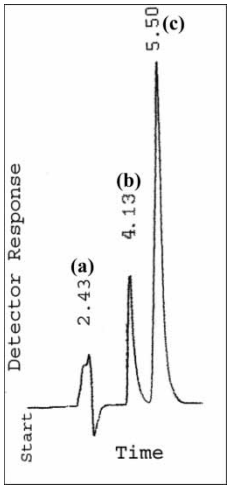


Figure 2. A chromatogram showing quetiapine in Seroquel tablets: (a) solvent front, (b) 4.0 μg/mL quetiapine, (c) 40 μg/mL temocapril.

the assay at the same concentration levels was found to be within 0.27–0.75 (n = 3).

The results of the proposed method were favorably compared with those obtained using the reference method.[4] Statistical analysis of the results obtained by the proposed and reference methods showed no significant

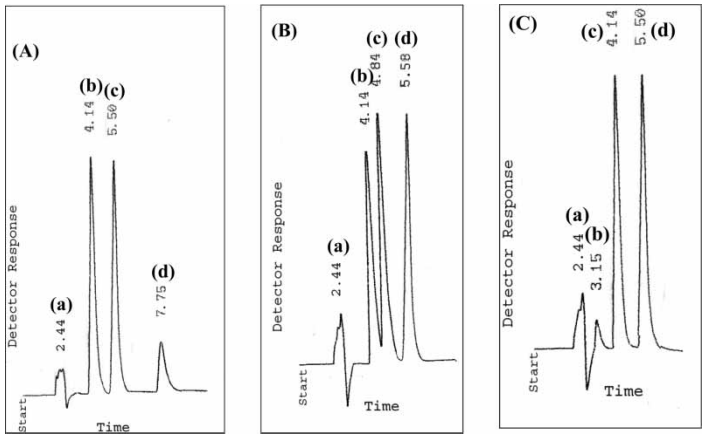


Figure 3. A chromatogram showing quetiapine with its coadministered drugs: (A) (a) solvent front, (b) 10 μg/mL quetiapine, (c) 40 μg/mL temocapril, (d) 10 μg/mL clomipramine. (B) (a) solvent front, (b) 10 μg/mL quetiapine, (c) 16 μg/mL carbamazepine, (d) 40 μg/mL temocapril. (C) (a) solvent front, (b) 30 μg/mL fluconazole, (c) 40 μg/mL quetiapine, (d) 40 μg/mL temocapril.

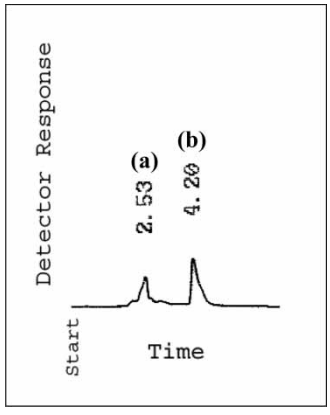


Figure 4. A chromatogram showing in plasma: (a) solvent front, (b) 2.0 μg/mL quetiapine.

difference in the performance of the two methods using student's t test and variance ratio F test (Table 6). The proposed procedure offers additional advantages over the reference procedure in that the former is more sensitive with good accuracy and precision. The latter method depends on determination of quetiapine spectrophotometrically using NaOH and measured at 246 nm.

Applications

Dosage Form Analysis

The proposed method was successfully applied to the assay of quetiapine in commercial tablets (Seroquel®). The average percent recoveries of different concentrations were based on the average of three replicate determinations. The results shown in Tables 7 are in good agreement with those obtained with the reference method.[4] Figure 2 shows a chromatogram indicating good resolved peaks of quetiapine. Degradation of quetiapine is easily detectable and can be determined quantitatively. Therefore, the proposed method can be used for the quality control of the tablets.

Co-administered Drugs

The proposed method allows determination of quetiapine in the presence of some co-administered drugs such as; the antidepressant clomipramine,[19] the mood stabilizing agent carbamazepine,[2,20] and the antifungal fluconazole,[2,21,22] as shown in Figure 3.

Table 8. Assay of quetiapine in spiked human plasma using the proposed method

Concentration taken (μg/mL)	Concentration found (μg/mL)	Recovery (%)
0.08	0.0778	102.75
0.10	0.0973	102.74
0.20	0.1979	101.06
0.50	0.4962	100.76
0.80	0.8089	98.90
1.0	1.0079	99.21
2.0	1.9938	100.31
Mean recovery		100.82
Standard deviation		1.53
%Error		0.57

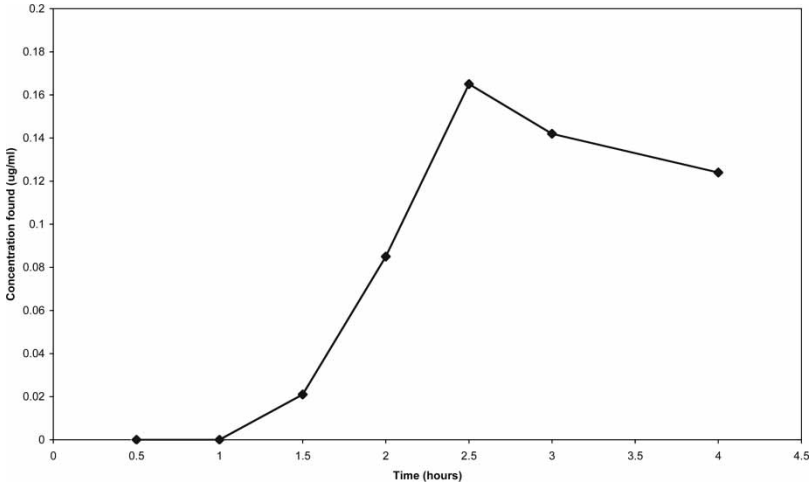


Figure 5. Monitoring of the blood level of quetiapine in patient plasma samples.

Human Plasma Spiking

Figure 4 shows the quetiapine peak obtained from spiked plasma. Table 8 shows the results obtained from spiked plasma. Under the above described experimental conditions, a linear relationship was established by plotting quetiapine concentrations against peak area for quetiapine. The concentration range was found to be 0.08–2 μg/mL. Linear regression analysis of the data gave the following equation:

$$A = 719.25 + 31939.75C \quad (r = 0.9999)$$

where: C is the concentration of quetiapine in μg/mL and A is the peak area.

The high value of the correlation coefficient (r- values > 0.999) indicates the good linearity of the calibration graph. Statistical analysis of the data gave the standard deviation of the residuals, ($S_{y/x}$) 207.24, of slope, (S_b) 123.46, and of intercept, (S_a) 368.21, and the % relative error, (%Er) 0.57%.[17]

Patient Samples

The plasma samples obtained from the volunteer were investigated using the previously obtained calibration graph or regression equation and the results obtained are shown in Figure 5, showing the maximum plasma level reached after 2.5 hours. Hence, the proposed method allows for the therapeutic drug monitoring of quetiapine level in plasma.

CONCLUSION

The proposed method for the determination of quetiapine based on the use of liquid chromatography with spectrophotometric detection was shown to be reliable, simple, accurate, sensitive, and precise. Moreover, the method is fast and feasible. The proposed method was found to have a limit of detection of 0.03 μg/mL and a limit of quantitation of 0.08 μg/mL.

The proposed method is stability indicating, as it is suitable for the determination of quetiapine in the presence of two of its degradation products; quetiapine N-oxide and quetiapine lactam. In addition, it is suitable for the determination of quetiapine in commercial tablets. Thus, it can be used for the quality control of quetiapine tablets. It also offers the possibility to determine quetiapine in the presence of the co-administered drugs; clomipramine, carbamazepine, and fluconazole. The proposed procedure is also suitable for the analysis of quetiapine in human plasma and it seems to be very promising for the therapeutic drug monitoring of patients undergoing chronic treatment with quetiapine.

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