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Development and validation of an LC–MS/MS method for the determination of quetiapine and four related metabolites in human plasma

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ABSTRACT

Pharmacokinetic measurement of the psychotropic compound quetiapine and four related metabolites in human plasma was conducted using a sensitive and specific liquid–chromatography tandem mass spectrometry (LC–MS/MS) assay that has been developed and validated for this purpose. The assay employs a single liquid–liquid extraction of quetiapine and its N-desalkyl (norquetiapine, M211,803, M1), 7-hydroxy (M214,227, M2), 7-hydroxy N-desalkyl (M236,303, M3), and sulfoxide (M213,841, M4) metabolites from human plasma, and utilizes dual-column separation, using Luna C_{18} columns (50 mm × 2.0 mm, 5 μm) and positive ionization tandem MS detection in the multiple reaction monitoring (MRM) mode of the analytes and their respective stable labeled internal standards. The method provides a linear response from a quantitation range of <0.70 ng/ml to at least 500 ng/ml for each analyte using 40 μl of plasma. The applicable range was extended by dilution up to 100-fold with blank matrix. The accuracy and precision for quetiapine were less than 6.0% and 6.4% for quetiapine, respectively. The accuracy (and precision) was less than 9.4% (5.9%) for norquetiapine; 6.4% (6.2%) for M2; and 10.0% (6.4%) for M3; and 8.6% (9.5%) for M4. This methodology enabled the determination of the pharmacokinetics of quetiapine and its metabolites in human plasma, and an example of its application is presented.

1. Introduction

Quetiapine fumarate (Seroquel®, ICI204,636) is a psychotropic compound approved for the treatment of schizophrenia [1–6], acute mania [7–12], and acute bipolar depression in adult patients [13–15]. Quetiapine ([2-(2-[4-(dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl] ethoxy) ethanol], Fig. 1) fumarate is extensively metabolized in the liver by the cytochrome P450 (CYP) isoenzyme 3A4, and the major metabolites circulating in the blood are the sulfoxide (M4) and carboxylic acid metabolites, which are excreted in urine and feces [16]. Other circulating metabolites include 7-hydroxy quetiapine (M2), norquetiapine (N-desalkyl quetiapine, M1) and 7-hydroxy, N-desalkyl quetiapine (M3) [17] as shown in Fig. 1.

Preclinical research has shown that quetiapine and norquetiapine have a combination of effects on several central neuroreceptors, including moderate antagonist affinity for dopamine D_2 and serotonin $5HT_{2A}$ receptors and mild to moderate affinity for $5HT_{1A}$ receptors. Norquetiapine is also a potent inhibitor of the norepinephrine transporter (NET) [18]. Imaging using positron emission tomography (PET) in non-human primates has extended these findings to include occupancy at D_2, $5HT_{2A}$, and NET at clinically relevant plasma levels [19]. Interactions with the three principal neurotransmitter systems involved in psychosis and mood disorders (dopamine, serotonin, and noradrenaline) may explain the broad spectrum of efficacy demonstrated for quetiapine fumarate in the treatment of psychiatric disorders.

To investigate the pharmacokinetics (PK) of quetiapine and four of its metabolites in humans, a sensitive and specific assay was required. An early high-performance liquid chromatographic (HPLC) method, performed well for quetiapine, but lacked sensitivity to support low-dose studies, while a gas chromatographic method with mass-selective detection (GC/MSD) afforded sensitivity, but lacked ruggedness [20]. A sensitive and specific HPLC assay utilizing ultraviolet and electrochemical detection to measure quetiapine and two metabolites was developed, validated, and used to support a majority of the clinical bioanalyses for studies conducted as part of quetiapine fumarate registration [21], but none of these methods measured norquetiapine. With the advent of robust LC–MS/MS procedures, this bioanalytical technology was successfully explored and incorporated [22]. A recent LC–MS/MS method measures quetiapine [23] but lacks

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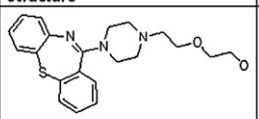
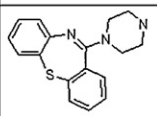
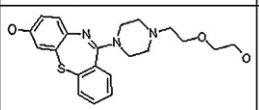
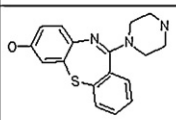
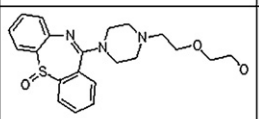
Compound	Structure	Molecular weight	Log D (7.4)	pKa 1	pKa 2
Quetiapine		383.51	1.55	5.8	5.0
Norquetiapine (M211,803, M1)		295.41	1.64	8.1	5.2
7-hydroxy-quetiapine (M214,227, M2)		399.51	0.80	6.4	5.0
7-hydroxy, N-desalkyl quetiapine (M236,303, M3)		311.41	0.90	8.0	6.0
Quetiapine sulfoxide (M213,841, M4)		399.51	-0.52	5.7	NA

Fig. 1. Structure of quetiapine and its metabolites.

the ability to measure norquetiapine, which is, at least in part, responsible for quetiapine's anxiolytic and antidepressant activity [24].

The use of a dual-column HPLC system, with gradient or isocratic options, allows for improved assay performance over a wide concentration range, flexibility, and throughput, and has led to the LC–MS/MS method presented here for the analysis of quetiapine and multiple metabolites in human plasma, including the first detailed technique for the quantitation of norquetiapine.

This LC–MS/MS procedure has been successfully validated, with a quantitation range of <0.70 ng/ml to at least 500 ng/ml for each analyte using a 40 μl aliquot of human plasma. The applicable range can be extended up to 100-fold by dilution with blank matrix. The assay employs a single liquid–liquid extraction of quetiapine, norquetiapine (N-desalkyl quetiapine, M211,803, M1), 7-hydroxy quetiapine (M214,227, M2), 7-hydroxy, N-desalkyl quetiapine (M236,303, M3), and quetiapine sulfoxide (M213,841, M4) from human plasma, and utilizes dual-column separation and positive ionization tandem MS detection of the analytes and their respective stable labeled internal standards (ISTDs). An example of the application of this methodology to the determination of the PK profiles of quetiapine and its metabolites in human plasma is presented.

2. Experimental

2.1. Chemicals and reagents

Quetiapine fumarate, its metabolites (norquetiapine, M2, M3, and M4) and the corresponding stable labeled ISTDs ($^{13}C_6$-quetiapine, d_8-norquetiapine, d_8-M2, d_8-M3, and d_8-M4) were synthesized at AstraZeneca. Acetonitrile, methanol, and isopropyl alcohol were all HPLC grade and purchased from Burdick & Jackson (Muskegon, MI, USA), reagent grade ammonium formate, trace metal grade ammonium hydroxide, HPLC grade methyl-*t*-butyl ether from Fisher Scientific (Pittsburgh, PA, USA), formic acid from Sigma–Aldrich (St. Louis, MO, USA), and HPLC grade triflouroacetic acid from Pierce Chemical Co. (Pittsburgh, PA, USA). Water was generated from an in-house purification system and used throughout the analysis. Human K_2EDTA plasma was purchased from Biochemed, Inc.

2.2. Instrumentation

The HPLC system consisted of a Leap CTC HTS PAL autosampler (Leap Technologies, Carrboro, NC, USA) configured with two injection valves, a 100-μl syringe, a six port divert valve (VICI Valco Instruments, Houston, TX, USA), Shimadzu LC-20AD pumps (Columbia, MD, USA), and a Sciex API 4000™ triple quadrupole mass spectrometer with TurboIonspray (MDS Sciex, Canada). The chromatographic separation was achieved with two Luna C_{18} columns (50 mm × 2.0 mm, 5 μm, Phenomenex, Torrance, CA, USA).

2.3. Method development

Methyl-*t*-butyl ether, ethyl acetate, and hexane were evaluated as possible organic solvents for the liquid/liquid extraction of quetiapine and its metabolites from plasma. The methyl-*t*-butyl ether solvent was chosen because it provided superior recovery and precision for the analytes of interest. Chromatographic conditions were developed to optimize separation of the analytes and improve analyte specificity, as two metabolites had the same precursor ion. The chromatographic conditions were also evaluated with blank extracts for the presence of ionization suppression or enhancement at the retention times of the quantified analytes.

2.4. Chromatography conditions

In general, two columns were held at ambient temperature and two injectors were multiplexed together to collect a single chromatogram for all five analytes and their ISTDs. The divert valve was programmed to direct the effluent of each column at the times of interest toward the mass spectrometer. All of the analytes were collected using a single acquisition method initiated with the first of two injections. The autosampler program consisted of two 20-μl injections with a total run time of 6.4 min.

A portion of the reconstituted sample was injected via one injection valve onto the first column at ambient temperature for the separation and analysis of M2, M3, and M4 using a gradient HPLC program at 0.5 ml/min. The gradient started at an initial mixture of 84% ammonium formate buffer (pH 3.0; 10 mM) with 16% methanol, increased to 47% methanol at 1.8 min and then to 95% methanol at 3 min and was held for 1 min.

The separation and analysis of quetiapine and norquetiapine was conducted with a second injection of the same reconstituted sample. The second portion, injected immediately after the first, was directed to the second injection valve and column with an isocratic mobile phase consisting of 60% ammonium formate buffer (pH 3.0; 10 mM) with 40% methanol, flowing at 0.6 ml/min.

2.5. Mass spectrometry

Chromatographic detection was carried out using positive ionization with the TurboIonspray source with MRM and unit resolution. The monitored transitions are summarized in Table 1. All of the analytes of interest were monitored using a dwell time of 75 ms, and the ISTDs were collected using a 50 ms dwell time.

2.6. Preparation of standards, calibration, and quality control samples

All primary and secondary diluted analyte and ISTD solutions were prepared in 1:1 methanol:acetonitrile and stored in the refrigerator. Separate primary solutions were prepared for each analyte and then diluted into a single secondary solution (10.0 μg/ml for

Table 1
Analyte and internal standard relationships.

Compound	Precursor ion (Q1 *m*/*z*)	Product ion (Q3 *m*/*z*)	Internal standard	Precursor ion (Q1 *m*/*z*)	Product ion (Q3 *m*/*z*)	Injection period
Quetiapine	384	253	$^{13}C_6$-quetiapine	390	259	2
Norquetiapine	296	210	d_8-norquetiapine	304	210	2
M2	400	269	d_8-M2	408	302	1
M3	312	226	d_8-M3	320	226	1
M4	400	221	d_8-M4	408	254	1

quetiapine and M3, 13.8 μg/ml for norquetiapine, 12.2 μg/ml for M2, and 12.3 μg/ml for M4). The calibration curve standards and quality control (QC) samples were prepared from separate solutions. The ISTD solution added to the individual samples was generated through the dilution of primary solutions to the final concentration of 5.00 ng/ml $^{13}C_6$-quetiapine, 10.0 ng/ml d_8-M4, and 50.0 ng/ml d_8-norquetiapine, d_8-M2 and d_8-M3.

The eight calibration standards and four QC pool samples were prepared in drug-free plasma with each sample consisting of at least 95% matrix. The calibration standards were prepared at concentrations ranging from 0.500 to 500 ng/ml for quetiapine and M3, 0.690 to 690 ng/ml for norquetiapine, 0.610 to 610 ng/ml for M2, and 0.615 to 615 ng/ml for M4. The calibration curves were plotted with the peak area ratio of each analyte and corresponding ISTD using a weighted ($1/x^2$) quadratic fit. Quality control samples were prepared at each respective lower limit of quantitation (LLOQ) and at three additional low, intermediate, and high concentrations which spanned the calibration range, as shown in Table 2.

2.7. Sample preparation and extraction

A 40-μl aliquot of each plasma sample was combined with 50 μl of an ISTD spiking solution and 50 μl of a 0.4N ammonium hydroxide solution and extracted with 700 μl of methyl-*t*-butyl ether. The mixture was vortexed to mix followed by centrifugation. A 300-μl portion of the organic layer was transferred to a clean 96-well reservoir and evaporated to dryness under a stream of nitrogen at approximately 40 °C. The dried extracts were reconstituted in 400 μl of an ammonium formate buffer (pH 3.0; 10 mM).

2.8. Validation procedure

The method's accuracy, precision, specificity, and recovery were demonstrated by a full validation using QC samples prepared at the LLOQ for each analyte and at low, middle, and high concentrations across the calibration range. Over-range QC samples were used to validate a dilution factor of 100. All matrix stability experiments were conducted at the low and high QC concentrations tested in six replicates at each stability condition. Calibration standards were spiked on the day of extraction with every batch containing matrix stability experiments.

2.8.1. Accuracy, precision, and specificity

Intra- and inter-assay precision, accuracy, and sensitivity were evaluated by comparing the mean measured concentrations of the QC sample with their nominal concentrations and the relative standard deviations of the QC samples. On at least four occasions, six replicates of each QC sample pool at the LLOQ, low, middle, and high concentrations were assayed.

The specificity of the method was established by assaying six lots of blank control matrix and comparing the response of each blank relative to the lowest calibration standards. The specificity

Table 2
Inter-day accuracy and precision of quetiapine and metabolite quality control samples.

Quetiapine	LLOQ 0.500 ng/ml	QC low 1.50 ng/ml	QC mid 120 ng/ml	QC high 380 ng/ml
Mean ± SD	0.530 ± 0.023	1.57 ± 0.10	124 ± 7	371 ± 10
% CV	4.3	6.4	5.5	2.7
% bias	6.0	4.7	3.3	−2.4
n	30	42	42	42
Norquetiapine	**LLOQ 0.692 ng/ml**	**QC low 2.08 ng/ml**	**QC mid 166 ng/ml**	**QC high 526 ng/ml**
Mean ± SD	0.757 ± 0.035	2.17 ± 0.13	171 ± 8	510 ± 17
% CV	4.6	5.9	4.8	3.3
% bias	9.4	4.3	3.0	−3.0
n	30	42	42	42
M2	**LLOQ 0.611 ng/ml**	**QC low 1.83 ng/ml**	**QC mid 147 ng/ml**	**QC high 465 ng/ml**
Mean ± SD	0.65 ± 0.04	1.9 ± 0.1	149 ± 8	447 ± 16
% CV	6.2	6.7	5.2	3.6
% bias	6.4	3.8	1.4	−3.9
n	24	36	36	36
M3	**LLOQ 0.500 ng/ml**	**QC low 1.50 ng/ml**	**QC mid 120 ng/ml**	**QC high 380 ng/ml**
Mean ± SD	0.55 ± 0.04	1.59 ± 0.09	123 ± 7	368 ± 13
% CV	6.4	5.9	5.5	3.5
% bias	10.0	6.0	2.5	−3.2
n	24	36	36	36
M4	**LLOQ 0.615 ng/ml**	**QC low 1.84 ng/ml**	**QC mid 148 ng/ml**	**QC high 467 ng/ml**
Mean ± SD	0.668 ± 0.058	1.89 ± 0.18	148 ± 9	455 ± 19
% CV	8.6	9.5	6.2	4.2
% bias	8.6	2.7	0.0	−2.6
n	24	42	42	42

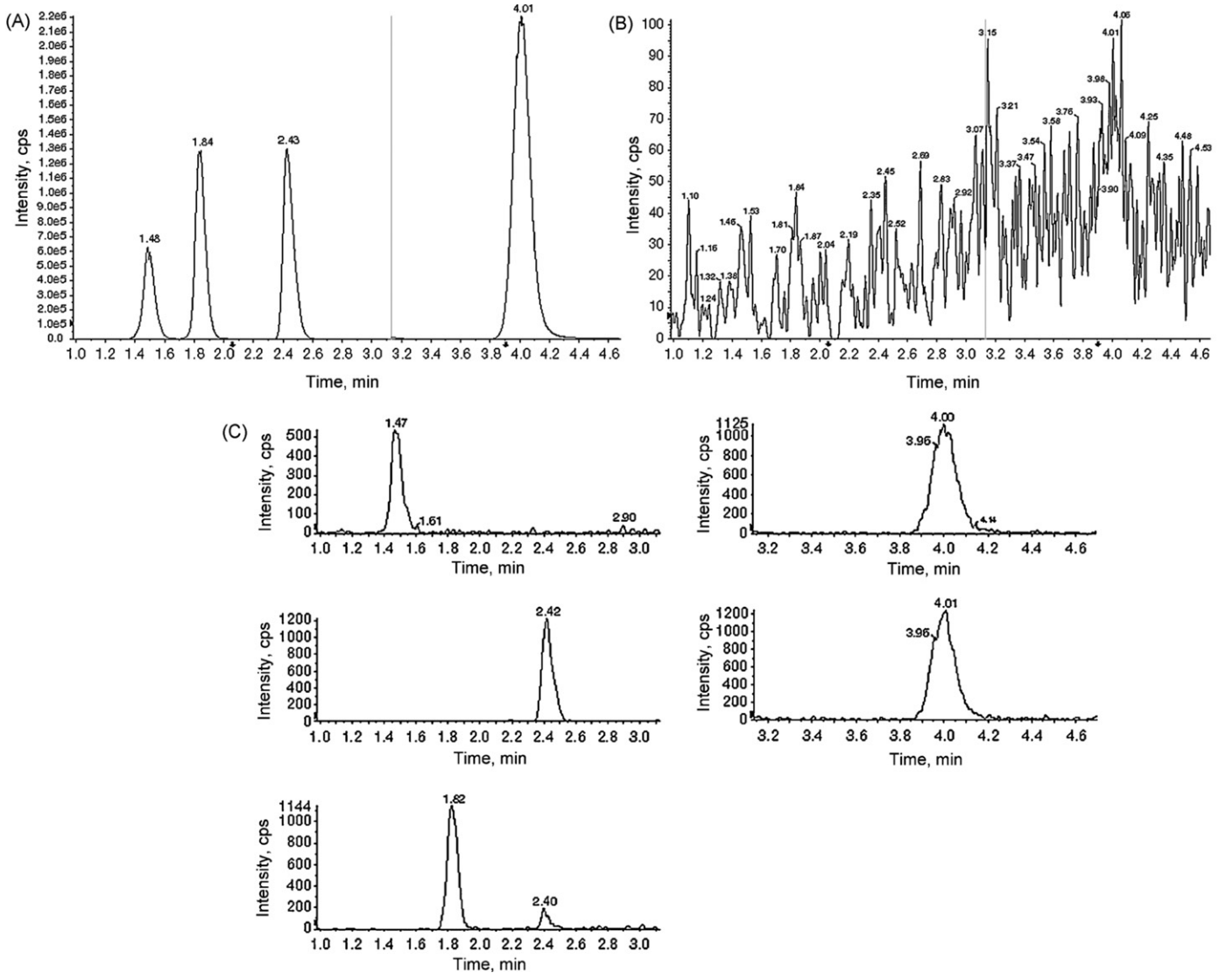


Fig. 2. Total ion chromatograms of quetiapine and metabolites at the upper and lower quantitation limits and of analyte-free plasma. (a) Total ion count at the upper limit of the calibration curve (L to R, M3, M2, M4, quetiapine + norquetiapine). (b) Total ion count of analyte-free plasma. (c) Individual *m*/*z* transition for each analyte at the LLOQ with 2 smooths (L to R, M3, quetiapine, M4, norquetiapine and M2).

was further investigated by preparing six QC pools (one replicate of each) in the middle range of the calibration curve from individual matrix donors and comparing the measured concentrations to the nominal concentrations.

2.8.2. Recovery and stability

Absolute recoveries were determined by comparing the measured peak areas of normal QC samples with those of blank sample extracts reconstituted with standard solutions prepared at the expected final extract concentrations. The matrix stability experiments included an evaluation of low and high QC pool concentrations held at room temperature for approximately 24 h, QC samples after five freeze–thaw cycles (−20 °C), and at least 70 days of −20 °C long-term storage stability.

3. Results and discussion

3.1. Chromatography

The use of a single C_{18} column (50 mm × 2.0 mm, 5 μm) with a gradient program yielded acceptable resolution between quetiapine and its 7-hydroxy (M2), 7-hydroxy-N-desalkyl (M3), and sulfoxide (M4) metabolites. However, an unacceptable level of carryover for norquetiapine was observed over the desired range of analysis as a result of the gradient conditions used.

To minimize norquetiapine carryover levels, the chromatography was divided into two HPLC systems, using an identical second column with isocratic elution. The first system separated the first three eluting metabolites, using a gradient to obtain the required resolution, and monitoring the *m*/*z* transitions of M2, M3, and M4 and their respective deuterium labeled ISTDs. At 3 min 10 s, the flow into the detector was diverted from the first HPLC system to the second system. At the same time the *m*/*z* transitions monitored changed to those of quetiapine, norquetiapine, and their corresponding ISTDs. While the eluent from the second column was being monitored by MS, a high organic mobile phase and multiple injector valve rotations (injections) were passed through the first system. The MS signal of the coeluting quetiapine and norquetiapine was not adversely influenced by ion suppression, enhancement, or within-source conversion.

The separation of the chromatography into two HPLC systems permits the analysis of quetiapine and its four metabolites within

Table 3
Dilution integrity.

Analyte	Quetiapine	Norquetiapine	M2	M3	M4
Theoretical conc. (ng/ml)	2000	2770	2450	2000	2460
Intra-run mean (ng/ml)	2010	2800	2470	2030	2520
n	6	6	6	6	6
Intra-run SD	48.9	51.4	37.6	37.4	75.4
Intra-run % CV	2.4	1.8	1.5	1.8	3.0
Intra-run % bias	0.5	1.2	1.0	1.5	2.5

a cycle time of 6.3 min, or the use of only the isocratic HPLC system to analyze quetiapine and norquetiapine with a cycle time of 4.2 min.

Typical chromatograms of the total ion count at the upper limit of the calibration curve (a), total ion count of analyte-free plasma (b), and individual *m*/*z* transition for each analyte at the LLOQ (c) are presented in Fig. 2.

3.2. Method validation

3.2.1. Accuracy and precision

Both accuracy and precision throughout the method's entire range were within acceptable bioanalytical limits. The intra-assay precision was evaluated through four method-performance batches. Quetiapine and norquetiapine data includes an additional method-performance batch used to prove the feasibility of using the isocratic chromatography part to analyze these two analytes only. The accuracy and precision, expressed as % bias and coefficient of variation (% CV), respectively, for quetiapine were less than 6.0% and 6.4%, respectively. The accuracy (and precision) was less than 9.4% (5.9%) for norquetiapine; 6.4% (6.2%) for M2; 10.0% (6.4%) for M3; and 8.6% (9.5%) for M4. Over-range QCs presented a % bias less than 2.5% with a % CV of less than 3.0%. Table 2 summarizes the mean values of accuracy and precision for inter-day assays run through the validation exercise, while dilution validation is presented in Table 3.

Table 4
Specificity determination for quetiapine and metabolites.

Analyte	Quetiapine	Norquetiapine	M2	M3	M4
Theoretical conc. (ng/ml)	120	166	147	120	148
Mean conc. ± SD (ng/ml)	118 ± 2	161 ± 2	139 ± 3	118 ± 2	144 ± 4
% CV	1.8	1.3	2.0	1.3	2.6
% bias	−1.7	−3.0	−5.4	−1.7	−2.7

3.2.2. Specificity of the method

No interfering peaks eluting at the retention times of quetiapine, its metabolites, or their respective stable isotope labeled ISTDs, were detected in the blank samples prepared from plasma from six different individuals. The analyte peaks from the calibration standard samples at the limit of quantification level presented a signal-to-noise ratio of at least 90.

Matrix effects were further investigated by spiking quetiapine and the four studied metabolites at the middle QC concentration level into six different plasma lots and comparing the measured concentrations to the nominal concentrations. Table 4 summarizes these results. The % CV between the concentration measured for the six different spiked QC specificity samples was at most 2.6% with a bias no greater than −5.4% of the theoretical concentration value, indicating there is no significant matrix effect.

3.2.3. Recovery

Absolute recoveries were determined by comparing the measured peak areas of normal QC samples with those of blank sample extracts reconstituted with standard solutions prepared at the expected final extract concentrations. The recovery for each analyte (and corresponding ISTD) were as follows: quetiapine, 95.5% (88.6%); norquetiapine, 85.9% (79.3%); M2, 87.0% (75.9%); M4,

Table 5
Stability determinations for quetiapine and metabolites.

	Long-term		Short-term (room temperature, 24 h)		Processed sample stability (228 h)		Freeze–thaw	
	Low QC sample	High QC sample	Low QC sample	High QC sample	Low QC sample	High QC sample	Low QC sample	High QC sample
Quetiapine								
Theoretical (ng/ml)	1.50	380	1.50	380	1.50	380	1.50	380
Mean ± SD	1.56 ± 0.04	372 ± 15	1.64 ± 0.05	371 ± 6	1.44 ± 0.05	371 ± 8	1.51 ± 0.03	375 ± 4
% CV	2.5	4.0	2.9	1.6	3.5	2.1	2.1	0.9
% bias	4.0	−2.1	9.3	−2.4	−4.0	−2.4	0.7	−1.3
Norquetiapine								
Theoretical (ng/ml)	2.08	526	2.08	526	2.08	526	2.08	526
Mean ± SD	2.17 ± 0.05	512 ± 28	2.22 ± 0.08	486 ± 14	1.98 ± 0.10	503 ± 9	2.04 ± 0.02	513 ± 13
% CV	2.3	5.5	3.6	2.9	4.9	1.8	1.1	2.5
% bias	4.3	−2.7	6.7	−7.6	−4.8	−4.4	−1.9	−2.5
M2								
Theoretical (ng/ml)	1.83	465	1.83	465	1.83	465	1.83	465
Mean ± SD	1.88 ± 0.07	449 ± 28	1.98 ± 0.03	443 ± 8	1.76 ± 0.05	432 ± 16	1.78 ± 0.06	436 ± 11
% CV	3.5	6.3	1.3	1.8	2.7	3.7	3.2	2.5
% bias	2.7	−3.4	8.2	−4.7	−3.8	−7.1	−2.7	−6.2
M3								
Theoretical (ng/ml)	1.50	380	1.50	380	1.50	380	1.50	380
Mean ± SD	1.58 ± 0.04	377 ± 16	1.59 ± 0.07	361 ± 7	1.39 ± 0.03	336 ± 13	1.44 ± 0.06	363 ± 7
% CV	2.3	4.4	4.3	1.8	1.9	4.0	4.2	1.8
% bias	5.3	−0.8	6.0	−5.0	−7.3	−11.6	−4.0	−4.5
M4								
Theoretical (ng/ml)	1.84	467	1.84	467	1.84	467	1.84	467
Mean ± SD	1.79 ± 0.09	457 ± 19	1.95 ± 0.06	443 ± 20	1.82 ± 0.08	456 ± 15	1.83 ± 0.07	465 ± 5
% CV	5.2	4.2	3.3	4.6	4.1	3.3	3.6	1.1
% bias	−2.7	−2.1	6.0	−5.1	−1.1	−2.4	−0.5	−0.4

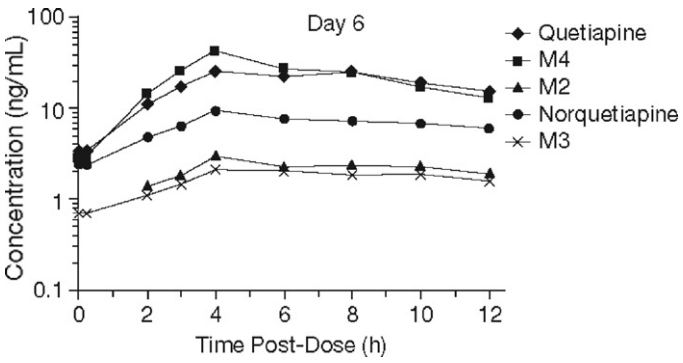


Fig. 3. Pharmacokinetic profile of quetiapine and its metabolites on day 6 from an adult subject who received a 50-mg dose of quetiapine XR.

78.0% (71.9%); and M3 with the lowest mean recovery of 68.8% (56.6%).

3.2.4. Stability

The stability of quetiapine and four of its metabolites in plasma, under various process and storage conditions, was investigated. The results of these experiments are summarized in Table 5.

Long-term storage stability was assessed by analyzing QC samples stored at $-20 \pm 10\,^{\circ}C$ for an extended period of time. Quetiapine, norquetiapine, M2, and M3 are stable for at least 119 days while M4 is stable for at least 77 days under these conditions. Long-term storage stability of these analytes for up to 18 months at $-20\,^{\circ}C$ has been established previously by a prior method [unpublished data].

Room temperature and freeze–thaw cycle stability were assessed by the analysis of QC samples held at room temperature for approximately 24 h, or QC samples subjected to five freeze–thaw cycles ($-20\,^{\circ}C$). The five analytes were stable under these conditions.

The stability of the processed samples was evaluated by leaving two sets of QC samples at room temperature for 228 h and quantitating the stored samples from freshly prepared calibration standards. There was no evidence to indicate lack of stability for the analytes under these conditions.

3.3. Cross-validation study

The pharmacokinetics of immediate release (IR) and extended release (XR) quetiapine fumarate and several metabolites have been characterized previously [25,26]. To demonstrate the utility of this methodology for the measurement of quetiapine and its four metabolites in human plasma, the plasma concentration-time profiles shown in Fig. 3 were generated as part of a cross-validation study using 20 incurred samples from a previously reported clinical trial to assess the effect of a light meal on the pharmacokinetics of quetiapine XR and its metabolites [27]. The average percent bias for this method from the previously assayed samples was −0.9%, 3.3%, 4.7%, and −10.1% for quetiapine, norquetiapine, M2, and M4, respectively. M3 was not analyzed by the prior method.

4. Conclusion

The validated method described here, utilizing a dual-column separation and positive ionization tandem MS detection, allows for the rapid determination of quetiapine and four of its metabolites in human plasma. The method is robust, selective, and sensitive, with a bioanalytical range over three orders of magnitude, and therefore, is suitable for use in PK studies. The option of an isocratic configuration gives the flexibility for rapid analysis of quetiapine and norquetiapine, and has been successfully used to determine their plasma concentrations in recent clinical trials.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

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