MANTECH Publications

Journal of Pharmaceutical Chemistry and Drug formulation
Volume 1, Issue 1, January-April, 2019

Quantification of Quetiapine Fumarate in Human Plasma by Rapid Liquid Chromatography and mass spectrometric method

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Abstract

A straightforward, quick, touchy and particular Liquid Chromatography couple mass spectrometric technique for the evaluation of quetiapine fumarate in human plasma is depicted. Analyte was chromatographed on an excellent essential C18 segment (50×4.6 mm) 3µm [Chromatopack] with isocratic elution at a stream rate of 0.700 ml/moment and Quetiapine-D4 was utilized as the inward standard. The test includes a basic strong stage extraction system of 0.100mL human plasma and the investigation was performed on a triple-quadrupole couple mass spectrometer by MRM mode through electrospray ionization (ESI). The strategy was straight in the focus scope of 1004.176ng/ml - 5.038ng/ml.The inside and between-day exactness and precision of the quality control tests. The recuperation was 1.38 and 1.36 for Quetiapine fumarate and Quetiapine-D4, separately. The investigation time for each example was 2 min. The technique was profoundly reproducible and gave crests with amazing chromatography properties.

Keywords*: Quetiapine fumarate, Liquid Chromatography, mass spectrometric method, Schizophrenia, Human Plasma*

INTRODUCTION

Quetiapine fumarate, {2-[4-(dibenzo [b,f] [1,4] thiazepin-11-yl) piperazin -1-yl] ethoxy} ethanol, is an atypical antipsychotic sedative with an exceptional receptor-restricting profile having a place

with another synthetic class, the dibenzodiazepine subordinates. Quetiapine fumarate is a foe at an expansive scope of neurotransmitter receptors.

Quetiapine is utilized as a part of the treatment of schizophrenia or hyper scenes related with bipolar turmoil. These antipsychotics have a low frequency of additional pyramidal symptoms and tardive dyskinesias contrasted with more seasoned antipsychotics. (Quetiapine Fumarate, Seroquel®) is endorsed by the US Food and Drug Administration (FDA) in 1997.

Quetiapine fumarate is utilized by the liver and eleven affirmed metabolites of quetiapine have been distinguished. Quetiapine seems, by all accounts, to be the major flowing species in plasma. Not at all like different antipsychotics, for example, Olanzapine no impact of cigarette smoking on quetiapine leeway was watched. The pharmacokinetics of quetiapine are straight, and don't contrast amongst men and ladies.

Quetiapine fumarate is quickly ingested after oral organization, achieving top plasma fixations in around 1.5 hours. The bioavailability of quetiapine is negligibly influenced by organization with nourishment, with increments in Cmax of 25%, and zone under bend (AUC) of 15%. Quetiapine is 83% bound to plasma proteins.

The liver widely utilizes quetiapine by means of CYP3A4 sulfoxidation and oxidation. The two metabolites are pharmacologically idle. The mean disposal half life is 2-3 hours. Leeway of quetiapine was diminished by up to 40% in the elderly. Quetiapine's overdoses were accounted for in 6 cases amid pre-promoting trial with assessed measurements running from 1200 to 1900 mg and no fatalities.

Numerous strategies have been utilized to decide quetiapine in human in natural materials incorporating HPLC with UV. Electrospray ionization MS.Pair MS/MS. UPLC with pair MS GC. A few HPLC strategies for the assurance of QUE have been accounted for. A large portion of these require bright identification, as QUE isn't electro dynamic. Be that as it may, none of these techniques is sufficiently delicate for assurance of the normal medication levels and some of them are tedious and require complex example pretreatment or long run circumstances. A few gas chromatography– mass spectrometry (GC– MS) techniques have

additionally been utilized, however here QUE should be derivatized before investigation. The main paper contrasts HPLC techniques and bright and MS/MS location.

Despite the fact that the example readiness is completely computerized, the run time is 35 min, in this manner the strategy permits assurance of just 40 tests per day, which isn't sufficient for routine examination and business use in pharmacokinetic considers. The following paper portrays HPLC– MS technique for synchronous assurance of Clozapine, Olanzapine, Risperidone, and QUE in plasma. All things considered, this technique requires two stage extractions and LOQ is too high for our motivation.

The objective of our work was to build up a HPLC– MS/MS strategy for assurance of QUE in human plasma got in a pharmacokinetic think about and to utilize the outcomes for assessing pharmacokinetic parameters.

Drug Profile

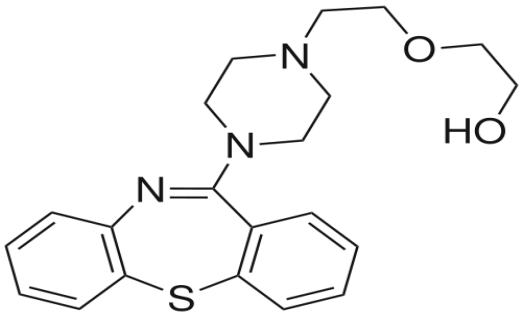
Generic name: Quetiapine

Brand name: Seroquel

Seroquel-XR

Physical State: White to off-white crystalline powder

STRUCTURE



IUPAC Name: {2-[4-(dibenzo [b, f] [1, 4] thiazepin-11-yl) piperazin-1-yl] ethoxy} ethanol

Molecular Formula: C21H25N3O2S

Formula Weight : 883.10

Molecular Weight : 767.04

Melting Point : 172-174 0C

Solubility : Soluble in Water

Indications and Uses

Quetiapine fumarate is indicated for the treatment of schizophrenia and the acute treatment of manic episodes associated with bipolar I disorder both as monotherapy and as an adjunct to lithium or divalproex.

Pharmacodynamics

Quetiapine fumarate is a psychotropic specialist having a place with the synthetic

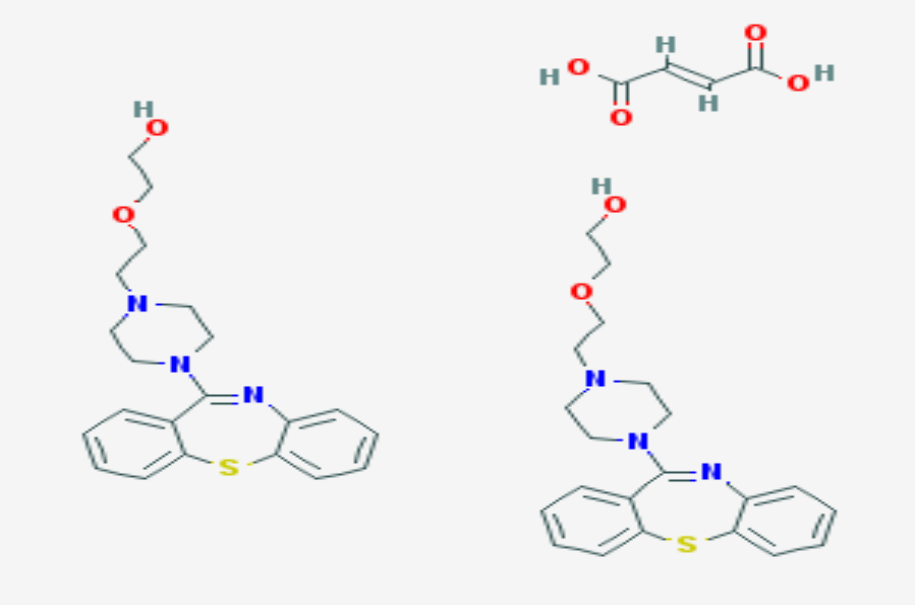
class of benzoxazole subordinates and is demonstrated for the treatment of schizophrenia. Quetiapine fumarate is a particular monoaminergic rival with high partiality for the serotonin Type 2 (5HT2), and dopamine composes 2 (D2) receptors. Quetiapine fumarate is an enemy at serotonin 5-HT1A and 5HT2, dopamine D1 and D2, histamine H1, and adrenergic alpha 1 and alpha 2 receptors. Quetiapine fumarate has no huge partiality for cholinergic muscarinic or benzodiazepine receptors.

Tiredness and orthostatic hypotension related with utilization of quetiapine might be clarified by its enmity of histamine H1 and adrenergic alpha 1 receptors, separately. Quetiapine's hostility of adrenergic a1 receptors may clarify the orthostatic hypotension saw with this medication.

Pharmacology

Antipsychotic impacts, clearly caused by dopamine and Serotonin receptor barricade in the CNS

Structure



Uses: This solution is utilized to treat certain psychological/state of mind conditions, (for example, schizophrenia, bipolar confusion, sudden scenes of lunacy or sorrow related with bipolar turmoil). Quetiapine is known as a hostile to maniacal medication (atypical compose). It works by re-establishing the adjust of

certain characteristic substances (neurotransmitters) in the cerebrum. Quetiapine can help avert extreme emotional episodes or decline how frequently temperament swings happen.

Take this drug by mouth as coordinated by your specialist, typically 2 or 3 times every day with or without nourishment. For the treatment of sadness related with bipolar

Confusion, take this prescription by mouth as coordinated by your specialist, typically once day by day at sleep time.

Side Effects

Obstruction, languor, agitated stomach, tiredness, weight increase, obscured vision, or dry mouth may happen. On the off chance that any of these impacts hold on or compound, tell your specialist quickly. Wooziness or tipsiness may happen, particularly when you first begin or increment your measurements of this medication. Wooziness and tipsiness can build the danger of falling. Get up gradually when ascending from a sitting or lying position. Get medicinal help immediately in the event that you have any intense reactions, including: swooning, seizure, serious wooziness.

MATERIALS AND METHODS

Material used:

a) Quetiapine Hemi fumarate & Quetiapine- D4 fumarate Working or reference standard
b) Methanol [HPLC grade]
c) Ammonium format [GR grade]
d) Acetonitrile [HPLC grade]
e) Milli-Q-Water/ HPLC grade water
f) Orochem Cartridge (Reverse phase-30mg,1ml DVB-LP)
g) Formic acid
h) Human Plasma (K3EDTA)

Preparation of Reagents used during the sample Analysis:

1) 5mM Ammonium Format Buffer:

Weight approximately 0.3153gm of ammonium format; dissolve in 1000ml of HPLC grade / Milli-Q-Water. Mix well and sonicate it and adjust pH-5.0 with formic acid.

2) Mobile Phase:

Take 700ml of Acetonitrile and 300ml of 5mM ammonium format buffer, mix well & sonicate it. Provide the batch number.

3) 0.1% Formic Acid

Take 100µl of formic acid make up volume with 100ml of HPLC grade/milli-Q Water. Mix well and sonicate it.

4) Diluent:

Take 250ml of methanol and 250ml of HPLC grade/milli-Q-Water, mix well

5) Auto Sampler Needle wash:

Weak Wash- Mobile phase

Strong Wash- Acetonitrile

Preparation of Quetiapine Stock Solution (1000µl/ml) and Dilution

Weigh approximately accurate 5.0gm of Quetiapine Hemi fumarate Working/Reference standard equivalent to Quetiapine and transfer it into 5.0 volumetric flasks and make volume up to 5ml with methanol then vortex and sonicate it, to produce the solution of ~ 1000.000µg/ml of Quetiapine.

Provide a batch number and store the stock solution in deep freezer at -200C ± 50C. Take 1.5ml of this solution and dilute upto 6.0ml with methanol: water (1:1) to produce ~ 250.000µg/ml solution. Provide a batch number and store it approximately at 2-80C in refrigerator. Prepare further spiking dilutions from this solution only.

Preparation of Quetiapine- D_4 stock and dilution preparation (ISTD)

Weigh approximately accurate 5.0mg of Quetiapine D4fumarate working/reference standard equivalent to Quetiapine- D4 and transfer it into 5.00ml volumetric flask and make volume up to 5ml with methanol then vortex and sonicate it, to produce the stock solution of ~ 1000.000µg/ml.

Dilute 0.5ml of this solution up to 25.0ml with Methanol: Water (1:1) to produce ~ 5000.000ng/ml solution. Make fresh solution every day from middle dilution to give final concentration ~ 500.000ng/ml of Quetiapine- D4. Store the stock solution and spiking solution approximately at 2-80C in refrigerator, Provide batch number.

Preparation of Calibration Curve Standards:

Preparation of spiking solution of Quetiapine

Prepare the following spiking solution with Methanol: Water (1:1) as described in below table.

Stock Concentration (ng/ml)	Stock Volume (ml)	Total volume after addition of Diluent (ml)	Spiking concentration (ng/ml)	Batch number
250043.8701	5.020	25.000	50208.8091	STD 1 SS
50208.8091	9.000	10.000	45187.9282	STD 2 SS

45187.9282	8.330	10.000	37641.5442	STD 3 SS
37641.5442	6.665	10.000	25088.0892	STD 4 SS
25088.0892	3.000	10.000	7526.4268	STD 5 SS
7526.4268	3.335	10.000	2510.0633	STD 6 SS
2510.0633	6.000	10.000	1506.0380	STD 7 SS
1506.0360	3.345	10.000	503.7697	STD 8 SS
503.7697	5.000	10.000	251.8849	STD 9 SS

Spiking of Quetiapine in Human Plasma:

Spike above spiking solution in Human plasma as per table below:

Spiking conc. (ng/ml)	Volume of spiking solutions (ml)	Total volume after addition of Human plasma (ml)	Final conc. In Human plasma (ng/ml)	Batch number
50208.8091	0.100	5.000	1004.176	STD 1 SM
45187.9282	0.100	5.000	903.759	STD 2 SM
37641.5442	0.100	5.000	752.831	STD 3 SM
25088.0892	0.100	5.000	501.762	STD 4 SM
7526.4268	0.100	5.000	150.529	STD 5 SM
2510.0633	0.100	5.000	50.201	STD 6 SM
1506.0360	0.100	5.000	30.121	STD 7 SM
503.7697	0.100	5.000	10.075	STD 8 SM
251.8849	0.100	5.000	5.038	STD 9 SM

Preparation of Quality control standards:

Preparation of spiking solution of Quetiapine:

Prepare the following spiking solution with methanol: water (1:1) as described in below table.

Stock Concentration (ng/ml)	Stock Volume (ml)	Total volume after addition of Diluent (ml)	Spiking concentration (ng/ml)	Batch number
250087.1078	5.020	25.000	50217.4913	STD 1 SS
50217.4913	8.200	10.000	41178.3428	HQC SS
41178.3428	6.100	10.000	25118.7891	MQC SS
25118.7891	1.000	10.000	2511.8789	INT DIL
2511.8789	3.000	10.000	753.5637	LQC SS
753.5637	3.350	10.000	252.4438	LLOQ QS SS

Spiking of Quetiapine in human plasma:

Spike above spiking solution in human plasma as per table below:

Spiking conc. (ng/ml)	Volume of spiking solutions (ml)	Total volume after addition of Human plasma (ml)	Final conc. In Human plasma (ng/ml)	Batch number
50217.4913	0.200	10.000	1004.350	STD 1 SM
41178.3428	0.200	10.000	823.567	HQC SM
25118.7891	0.200	10.000	502.376	MQC SM
2511.8789	0.200	10.000	50.238	INT DIL
753.5637	0.200	10.000	15.071	LQC SM
252.4438	0.200	10.000	5.049	LLOQ QS SM

Chromatographic Conditions:

HPLC: Water Acquity UPLC

Column: Peerless Basic C18 (50×4.6 mm) 3µm [Chromatopack]

Column oven: 40 0C ± 5 0

Mobile Phase: Acetonitrile (70%):5mM Ammonium format Buffer (30%)

Needle Wash: Weak wash- Mobile Phase
Strong wash- Acetonitrile

Detection: Q3 [Quattro premier and Quattro premier XE, WATERS, USA]

ION Mode: Positive Mode

Injection Volume: 10µl (Partial loop with needle overfill)

Sample cooler Temp*:* 10 0C ± 5 0C

Retention Time: Quetiapine around 1.38 minute Quetiapine D4 around 1.36 minute

Run Time: 2.0 minute

Flow rate: 0.700ml/minute

Mass Tune parameters optimize of LC-MS/MS

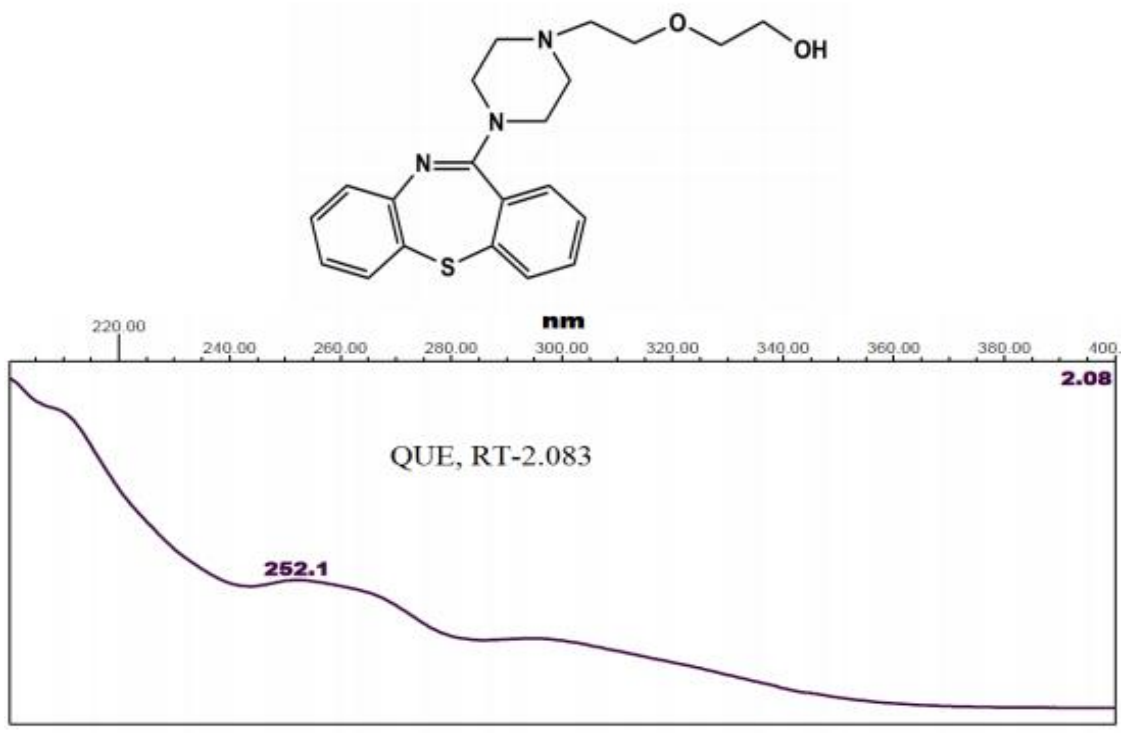
Sr. No.	Parameters	Drug (Quetiapine)	ISTD (Quetiapine-D_4)
1	Capillary (kV)	3.00	3.00
2	Source temperature	120 ^{0}C	120 ^{0}C
3	Desolvation Temp.	350 ^{0}C	350 ^{0}C
4	Cone (V)	35	36
5	LM resolution 1	15.0	15.0
6	HM resolution 1	15.0	15.0
7	Collision energy(eV)	22	24
8	Entrance	2	2

9	Exit	2	2
10	LM resolution 2	15.0	15.0
11	LM resolution 2	15.0	15.0
12	Detection	~384.22 > 253.14	~384.25 > 253.14
13	Dwell time	0.200 sec.	0.200 sec.
14	Desolvation gas flow	700	700
15	Cone gas flow	2.0	2.0
16	Ion energy 1	0.5	0.5
17	Ion energy 2	1.0	1.0

CALIBRATION CURVE

Quetiapine (QUE)

2-(2-(4-(dibenzo[*b*,*f*][1,4]thiazepin-11-yl)piperazin-1-yl)ethoxy)ethanol



[Chemical structures, IUPAC names and UV spectra of quetiapine and its impurities]

CONCLUSION

An inclination RP-UPLC technique is effectively produced for the estimation of quetiapine in pharmaceutical measurements frame. The strategy approval comes about have demonstrated that the technique is specific, exact, precise, straight, and strong, channel good and strength showing. The run time (5.0 min) empowers for fast assurance of medication. Additionally, it might be connected for assurance of QUE in the investigation of mix consistency, tablet content consistency and in-vitro disintegration profiling of QUE measurement shapes, where test stack is higher and high throughput is basic for quicker conveyance of results.

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