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QUETIAPINE FUMARATE ANALYSIS: A REVIEW OF CURRENT AND EMERGING TECHNIQUES

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ABSTRACT

Quetiapine fumarate, a dibenzothiazepine derivative, is classified as a second-generation antipsychotic drug used to treat schizophrenia. The current study primarily focusses on development of analytical and bioanalytical methods, along with several techniques established for the estimation of quetiapine fumarate, whether in bulk or pharmaceutical dose form. Although they enable us to use cutting-edge analytical equipment to acquire both qualitative and quantitative results, analytical methods are essential for determining compositions. The analytical method for quetiapine fumarate may be chromatographic, spectral or hyphenated. Understanding important process factors and reducing their impact on accuracy and precision are made easier with the help of these techniques. Development of analytical methods is necessary to maintain high standards for commercial product quality and to comply with legal obligations. The development of analytical techniques is essential to sustaining regulatory requirements and maintaining high standards for the quality of commercial products. Bioanalytical techniques are intended to quantify the concentration of drugs, metabolite, or usual biomarker present in different biological fluids, such as tissue extracts, urine, serum, and saliva.

KEYWORDS: Quetiapine fumarate, Bioanalytical method, HPLC, HPTLC, UV.

INTRODUCTION

The IUPAC name of Quetiapine fumarate is 2-[2-(4-benzo[b][1,4] benzothiazepin-6-ylpiperazin-1-yl) ethoxy] ethanol;(E)-but-2-enedioic acid (Figure 1).[1] The symptomatic treatment of schizophrenia necessitates the use of quetiapine. Moreover, it can be taken singly or in combination with other medications to treat acute manic or mixed episodes in bipolar disorder patients. It could be used for bipolar disorder for managing depressive periods. Apart from the aforementioned uses, quetiapine is also used in conjunction with antidepressants to treat serious depression.[2] 5-HT

1A and 5-HT2 receptor-mediated serotonin activity is antagonistic to quetiapine fumarate. Additionally, this agent reversibly binds to dopamine D1 and D2 receptors in the mesolimbic and mesocortical parts of the brain, but with a lesser affinity. This reduces the psychotic effects of the agent, such as delusions and hallucinations. Furthermore, alpha-1, alpha-2 adrenergic, and histamine H1 receptors are bound by quetiapine fumarate.[3] Following the administration of an oral dose, it is quickly and efficiently absorbed. Quetiapine fumarate has an 83% protein binding efficiency. The liver is where quetiapine is mostly metabolised. For this medication, oxidation and sulfoxidation are the primary metabolic routes. A dosage was found in the urine in around 73% of and the faeces in about 20%.[4] Quetiapine fumarate assay in dosage forms and pure form lacks an established Pharmacopoeia monograph for analytical technique.[5] However, there are many analytical methods were reported by different workers for its determination in pure form, formulations and in biological materials using spectrophotometry, chromatography and electrophoresis techniques.

Need of Analytical method

Official test methods are the end product of analytical technique development. As a result, quality control laboratories used these techniques to examine the performance, identification, purity, safety, and efficacy of drug items. Analytical techniques used in production are of the utmost relevance to regulatory bodies. The applicant must demonstrate control of the entire drug development process using approved analytical methods in order for regulatory authorities to approve the medicine.[6] Stability testing (Q1), validation of analytical techniques (Q2), impurities in drug substances and products (Q3), and specifications for new drug substances and products (Q6) are analytical guideline documents that the ICH recently issued.[7]

Analytical Method Development by UV Spectrophotometer

The study of interactions between matter and electromagnetic radiation in the ultraviolet-visible region is known as ultraviolet-visible spectroscopy. The range of wavelengths in the ultraviolet (UV) is 200–400 nm.[8] The Beer-Lambert law, which it is founded on, stipulates that the relationship between a solution's absorbance and path length is one of direct proportionality. As a result, it can be used to calculate the concentration of the absorber in a solution for a particular path length. It's critical to understand how quickly absorbance varies with concentration.[9]

Table no. 1: Analytical method development using UV spectrophotometer.

S. No.	Sample / Dosage form	Method / Instrument model	Solvent / Solution	Wavelength	References
1.	Tablet	Shimadzu UV-visible spectrophotometer 1800	0.1 N HCl	Second order derivative method 254.76nm	10
2.	Tablet	Shimadzu UV-visible spectrophotometer 1700	0.1 N HCl	Method A and Method B 209 and 208 nm	11
3.	Tablet	Shimadzu UV-visible spectrophotometer 1700	0.01 M acetous perchloric acid	Method A and Method B 222 nm	12
4.	Tablet	Shimadzu UV-visible spectrophotometer 1800	1,4-dioxane/acetone	Method A and Method B 410 and 380 nm	13

Analytical method development by HPLC

One of the most well-established analytical procedures and by far the most extensively used separation method is high performance liquid chromatography (HPLC). Over the past 40+ years, it has been utilised in labs all over the world for pharmaceutical sciences, clinical chemistry, food and environmental evaluations, synthetic chemistry, etc.[14] A liquid or a solid phase might be the stationary phase in this approach. The components of a combination can be separated via

HPLC using a liquid mobile phase. The phrase "high-performance liquid chromatography" (HPLC) refers to liquid chromatography in which the stationary phase is contained in a column and the liquid mobile phase is mechanically pumped through the column.[15] HPLC systems' beating heart is the column. A reproducible and symmetrical peak will be produced by a good silica and bonding procedure, which is required for precise certification. C18 (USP L1), C8 (USPL8), Phenyl (USP L11), and Cyno (USP L18) are examples of commonly used RP columns.[16]

Table no 2: Various types of columns and their applications.

Column	Phase	Solvent	Application
C_{18}	Octadecyl	ACN, MeOH, H_2O	General, nonpolar
C_8	Octyl	ACN, MeOH, H_2O	General, nonpolar
Phenyl	Styrl	ACN, MeOH, H_2O	Fatty acids, double bond
Cyano	Cyanopropyl	ACN, MeOH, H_2O, THF	Ketones, aldehydes
Amino	Aminopropyl	ACN, MeOH, H_2O, THF, $CHCl_3$, CH_2Cl_2	Sugars, anions

Table no 3: Analytical method developments using HPLC method.

S. No.	Sample	Stationary phase/column	Mobile phase	Wavelength (nm)	Flow rate (ml/min)	RT (min)	Reference
1.	Tablet	Thermo column Symmetry C18 (4.6 x 150mm, 5 µm)	Sodium dihydrogen phosphate and the pH was adjusted to 4.0 by Orthophosporic Acid & Methanol in the ratio of 35:65 v/v	290 nm.	1.0 ml/min	6 min	17
2.	Tablet	C18 column	Methanol: Acetonitrile: OPA 35:35:30 (v/v/v)	238nm	1ml min^{-1}	7.33 min	18
3.	Tablet	C18 column	Methanol: water 30:70 (v/v)	359 nm	-	5.27 min	19
4.	Tablet	Zorbax Eclipse Plus C8 Column (250×4.6mm, 5µ)	Di-ammonium Hydrogen Phosphate (0.02 M), methanol, and acetonitrile	230 nm	1.3 ml/min	-	20
5.	Tablet	C18 column (250 × 4.6 mm i.d., 5 µm)	Methanol: acetonitrile: water 67:16:17 v/v/v	220 nm	1 ml/min	5.35 min	21
6.	Tablet	Zorbax XDB C-18, 150 mm x 4.6 mm, 5.0 µm	Acetonitrile:Methanol: Buffer (275:275:450)	290 nm	-	10 min	22
7.	Tablet	Microsorb-MV 100-5 C-18 (250 x 4.6mm, 5 µm)	Acetonitrile and phosphate buffer (pH 3) in the ratio of 50:50 (v/v)	292 nm	1.0 ml/min	5.42 min	23
8.	Tablet	Inertsil ODS (250 x 4.6 mm, 5µ)	0.02%v/v formic acid and methanol 90:10 (v/v)	220 nm	1ml/min	13.4 min	24
9.	Tablet	X-bridge C18, 150x4.6 mm, 3.5 µm	5 mM ammonium acetate and Acetonitrile	220 nm	1.0 ml/min	5.5 min	25
10.	Tablet	Inertsil-3 C8, 150 mm × 4.6 mm, 5 µm	0.01 M di-potassium hydrogen orthophosphate (pH 6.8) and acetonitrile in the ratio of 80:20 (v/v),	217 nm	1.0 ml/min	-	26
11.	Tablet	C8 column	Acetonitrile (ACN), acetate buffer and triethylamine (TEA), (60% ACN, 39.8%	278 nm	1.0 ml/min	-	27

			acetate buffer and 0.2% TEA, v/v/v), adjusted to pH = 4.7 with acetic acid				
12.	Tablet	Zorbax C8 column (100 mm ×4.6 cm i.d., 3 µm particle)	0.15% Triethylamine (pH 6.0) and acetonitrile: methanol (80:20)	252 nm	1.2 ml/min	13 min	28
13.	Tablet	column Hypersil C18 (250×4.6mm, 5µm)	Acetonitrile and pH 3.0 phosphate buffer	210 nm	1.0 ml/min^{-1}	3.65 min	29
14.	Tablet	C18 column	Phosphate buffer pH 6.6: Acetonitrile: Methanol (45:40:15	220 nm	1.0 $ml\ min^{-1}$	-	30
15.	Tablet	Hibar R 250 × 4.6 mm HPLC column	Phosphate buffer: acetonitrile (55:45v/v)	254 nm	1.0 ml/min	4.458 mins	31
16.	Tablet	Phenomix Stainless Steel C18 (250 x 4.6 mm, 5 µ)	Phosphate buffer (pH 3), acetonitrile, methanol (50:40:10)	220 nm	0.8 ml/ min	4.69 min	32
17.	Tablet	C18 Waters column (75x4.6mm I.D., particle size 3.5 µm)	Phosphate buffer (pH 3.0 adjusted with orthophosphoric acid) and acetonitrile in the ratio 40:60 v/v	291 nm	0.8 mL/min	2.929 min	33
18.	Tablet	C18 column	Phosphate buffer, acetonitrile and methanol in the ratio 50:40:10v/v/v	245nm	1ml/min	5.08 min	34

Analytical Method Development Using HPTLC Method

HPTLC is a potent analytical technique that works well for both qualitative and quantitative tasks.[35] Depending on the type of adsorbents employed on the plates and the development solvent system, separation may be caused by partition, adsorption, or both phenomena. Principle, theory, instrumentation, implementation, optimization, validation, automation, and qualitative and quantitative analysis are some of the several facets of HPTLC basics.[36]

Table no 4: Major Differences between TLC & HPTLC.

Parameters	**TLC**	**HPTLC**
Technique	Manual	Instrumental
Efficiency	Less	High
Layer	Lab made	Precoated
Mean particle size	10-12 µm	5-6 µm
Layer thickness	250 µm	100µm
Plate height	30 µm	12 µm
Solid support	Silica gel, Alumina, Kieselguhr	Silica gel-Normal Phase C8 and C18-reverse phase
Spotting of sample	Manual (Capillary/Pipette)	Syringe
Volume of sample	1-5µL	0.1-0.5 µL
Separation	10-15 cm	3-5 cm
Separation time	20-200 min	3-20 min
Analysis time	Slower	Storage migration distance and the analysis time is greatly reduced
Scanning	Not possible	Use of UV/visible/fluorescence scanner

Table no 5: Analytical Method Development Using HPTLC Method.

S. No.	Sample	Stationary Phase/ Column	Mobile phase	Wavelength (nm)	Rf	Reference
1.	Bulk drug and formulation	Silica gel	Toluene–methanol 8:2 (v/v)	254 nm	0.37 ± 0.02	37
2.	Pure form and tablet formulations	Silica gel 60 F 254 HPTLC plates	Ethanol: water 9: 1 (v/v)	220 nm	0.55	38
3.	Pure form	Silica gel 60 F 254 HPTLC plates	Toluene–ethyl acetate–methanol (5.5:4.0:0.5, V/V)	290 nm	-	39
4.	Pure form	Silica gel 60 F 254 HPTLC plates	Toluene–methanol 7:4 (V/V)	290 nm	-	40
5.	Tablet	Aluminum plates precoated with silica gel 60F-254	Toluene: Ethyl acetate: Diethyl amine (5:3:2, v/v/v)	291 nm	0.54	41
6.	Pure form and tablet formulations	Silica gel 60F 254	Toluene:1,4-dioxane: dimethylamine (5:8:2, v/v/v)	225 nm	0.70	42
7.	Tablet	Silica F254 plates	Hexane–dioxane–propylamine 1:9:0.4 (v/v)	254 nm	0.56 ± 0.01	43

Bioanalytical Method Development

Bioanalysis is covering the identification and quantification of analytes in biological samples (blood, plasma, serum, saliva, urine, feces, skin, hair, organ tissue). Bioanalysis is not only measuring of small molecules such as drugs and metabolites but also to identify large molecules such as proteins and peptides. Bioanalysis is well established in pharmaceutical companies to support drug discovery and drug development. Bioanalysis has an important role to perform the toxicokinetic (TK), pharmacokinetic (PK) and pharmacodynamics (PD) studies of new drugs. Bioanalysis is also established in clinical, preclinical and forensic toxicology laboratories. Thus, bioanalysis is an important discipline in many research areas such as the development of new drugs, forensic analysis, doping control and identification of biomarkers for diagnostic of many diseases.[44,45]

Table no 6: Analytical Method Development Using HPTLC Method.

S. No.	Method	Sample/ dosage form	Stationary phase/column	Mobile phase	Wavelength (nm)	Flow rate min/ml	Retention time (min)	Reference
1.	TLC-densitometric and RP-HPLC	Rat plasma	TLC plates (20 × 10 cm) coated with 60 F254 silica gel 0.2 mm thickness XTerra C18 (4.6 mm× 250 mm, 5 µ)	Ethyl acetate: ethanol: ammonia solution 33% (8: 2:0.05, by volume) methanol: 0.05 M KH2PO4 (pH 4.3) (70:30, v/v)	240 nm	1 ml/min	8 min	46
2.	UHPLC- MS/MS	Human plasma	BEH Shield RP18 column (2.1 mm × 50 mm; 1.7 µm),	10 mM ammonium formate buffer pH 3.0 and acetonitrile 75:25 v/v	-	0.4 ml/min	3 min	47
3.	HPLC–MS/MS	Human plasma	Atlantis dC18 column (100	Acetonitrile–methanol–0.01 M	-	-	3 min	48

			mm × 3.0 mm, 3µm)	ammonium acetate (31:19:50, v/v/v); pH was adjusted with acetic acid (pH 3.5)				
4.	HPLC	Tablets and Human Plasma	Zorbax SB-Phenyl column 250 mm × 4.6 mm i.d., 5 mm particle size	Acetonitrile and 0.02 M phosphate buffer (50:50) at pH 5.5	254 nm	1 ml/min	-	49
5.	RP-HPLC	Human plasma	C18 (4.6 x 150mm, 5 µm)	Sodium Dihydrogen Phosphate: Methanol (35:65 v/v)	290 nm	1 ml/min	-	50
6.	LC–MS–MS	Human Plasma	C18 column	Acetonitrile–5 mM ammonium formate, pH adjusted to 4.5 with formic acid 85:15 (v/v)		0.5 mL /min-1	1.25 min	51
7.	LC–MS/MS	Human Plasma	C18 column (3.5 µm, 2.1 mm × 50 mm)	Acetonitrile/water (containing 10 mM ammonium acetate and 0.1% formic acid)	-	0.4 ml/min	3 min	52
8.	HPLC	Human Plasma	C18 column	Acetonitrile-methanol-10.4mM pH 1.9 phosphate buffer (17.5:20:62.5 v/v/v)	254 nm	1 ml min^{-1}	-	53
9.	Spectrofluori-metric	Human Plasma	-	-	510 nm	-	-	54
10.	LC-MS/MS	Rat plasma	C8 column	Diethyl ether: dichloromethane (70:30)	-	1 ml/min	-	55
11.	LC-MS/MS	Human Plasma	C18 column	10:75:15v/v mixture of ammonium formate buffer (5 mM, pH 4.50) and acetonitrile and methanol	-	0.4 mL/min	2.5 min	56
12.	HPLC–UV	Human Plasma	C8 column (150 mm × 4.6 mm i.d., 5µm)	Acetonitrile (30%) and a 10.5 mM, pH 3.5 phosphate buffer containing 0.12% triethylamine (70%)	245 nm	1.2 mL min^{-1}	-	57
13.	HPLC	Human Urine	ODS (250 mm × 4.6 mm i.d., 5 µm particle size)	Acetonitrile and 0.1% phosphate buffer (pH 3.1) (40:60)	240 nm	1 mL/min	-	58
14.	RP-HPLC	Whole Blood	C-18 column (150 mm × 4.6 mm, 5 µm)	Acetonitrile–methanol–0.025 M phosphate buffer (pH 2.5) 40:30:30%, v/v	-	1.2 mL min^{-1}	-	59

CONCLUSION

In this review, the various analytical and bioanalytical techniques utilized for the estimation of Quetiapine fumarate as well as in the bulk form of the medications have received the most attention. The development of analytical and bioanalytical techniques such as UV spectrophotometry, HPLC, HPTLC, RP-HPLC, LC-MS/MS and other techniques has been the focus of research. All of the established analytical techniques have increased levels of automation and processing of samples are very sensitive, reliable, reproducible, and precise. A literature review is conducted for collecting data on various instrumental analytical techniques. A unique analytical approach could be developed using such data.

Competing Interests

Authors report no conflict of interest concerning this review article.

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