CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com Review Article

A CONCISE REVIEW ON ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF OLANZAPINE

[1]Vijendra P. Rathod, [2]Rahul S. Wani, [3]Saurabh C. Khadse, [4]Atul A.Shirkhedkar
[1]M. Pharm student, Department of Pharmaceutical Chemistry, R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur, Dist. Dhule (MS), India 425 405.

Article Received: March 2019 **Accepted:** April 2019 **Published:** May 2019

Abstract:
Olanzapine (OLZ) is an atypical antipsychotic agent is and different antipsychotic agent medications like Carbamazepine, Fluoxetine hydrochloride, Simvastatin, Clozapine, paliperidone, Quetiapine, several beta blocker, Risperidone, 9-Hydroxyrisiperidone, Demethylolanzapine, Aripiprazole, Orphenadrine, 1,2 Naphthoquinone, P-dimethylamino Benzaldehyde, Cerium sulphate, N-bromosulphinimide. The present investigation assesses the various approaches for analysis of OLZ in bulk drug as well as their pharmaceutical formulations. A concise survey states the collection and outline of about 74 explanatory strategies which incorporates HPLC, HPTLC, UV-Spectrophotometry, electrochemical techniques, LC-MS/MS, techniques actualized for examination of OLZ in biological matrices, bulk samples and in different dosage forms. The review depicts the rate usage of the different methodologies for examination of OLZ. The measurable information concerning the utility of these strategies for estimation of OLZ distributed during 1995 to 2018 have been incorporated.

Keywords: *Olanzapine; HPLC; HPTLC; LC–MS/MS; Spectrophotometry.*

Corresponding author:
Mr.Vijendra P. Rathod,
M. Pharm student, Department of Pharmaceutical Chemistry
R.C. Patel Institute of Pharmaceutical Education and Research,
Shirpur, Dist. Dhule (MS), India 425 405.
Email id:vijendrarathod36@gmail.com, Mobile Number– 7350648486.

QR code

Please cite this article in press Vijendra P. Rathod et al., ***A Concise Review on Analytical Method Development and Validation of Olanzapine.,*** *Indo Am. J. P. Sci, 2019; 06(05).*

INTRODUCTION:

Olanzapine (OLZ) is an atypical antipsychotic agent and chemically it is (2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno [2, 3-b] [1, 5] benzodiazepine) is an (**figure 1**).**[1]** It has antipsychotic activity and the usual dose is 10 mg once daily and it is a white to off-white powder OLZ It is used in the treatment of depression. **[2].** Additionally, OLZ It decreases the gluconeogenesis while increasing the glucose uptake by muscles and fat cells. Olanzapine Works by blocking the receptors in the brain that are involved in transmitting these messages between the nerve cells. **[3].** It has a higher affinity for 5-HT2 serotonin receptors than D2 dopamine receptors. OLZ is extensively metabolised to form 10-N-glucuronide, 4′-N-desmethyl, 2-hydroxymethyl and 4′-N-oxide metabolites. Reacts with glucuronyltransferase to form a 10-N-glucuronide and a quaternary 4′-Nglucuronide. The cytochrome P450 (CYP) and (FMO) are responsible for OLZ metabolism. CYP1A2 and FMO3 form 4′-N-desmethyl olanzapine and olanzapine Noxide, respectively **(Figure 2).**The average concentrations of olanzapine 10-N-glucuronide and N-desmethyl olanzapine. 2-Hydroxymethyl olanzapine is a minor metabolite and is primarily formed by CYP2D6. John T. Callaghan, Richard F. Bergstrom, Louis R. Ptak, and Charles M. Beasley

OLZ is also available in combination with The OLZ in various dosage forms as single constituent and in combination with Carbamazepine, Fluoxetine hydrochloride, Simvastatin, Clozapine, paliperidone, Quetiapine, several beta blocker, Risperidone, 9-Hydroxyrisiperidone, Demethylolanzapine, Aripiprazole, Orphenadrine, 1,2 Naphthoquinone, P-dimethylamino Benzaldehyde, Cerium sulphate, N-bromosulphinimide. Although reviews about the pharmacology of OLZ have been earlier available, none of these reviews concentrated on OLZ analytical methods, perhaps because it is one of the bisystolic drug introduced in the market. The aim of this review is to deliver summary of the relevant published literature and a discussion of methods for the determination of OLZ on its own or in mixtures, in pure form, formulations, and biological samples using different analytical procedures (HPLC, HPTLC, UV, Bio analytical, LC-MS/MS, etc)

An extensive literature survey was done using the database like scholar, scifinder, Pubmed, Scopus and web of science. The literature survey revealed that the numerous analytical methods have been reported for OLZ such as high-performance liquid-chromatography, high-performance thin-layer chromatography, and Liquid chromatography coupled with mass spectrophotometry, ultraviolet and visible spectrophotometry. **[1-74].** Therefore, the aim of the proposed work to analysed and summarized all the analytical method exemplified in the literature. Taking into account of applicability of OLZ in the treatment of Antipsychotic. This analytical profile of OLZ focuses the analytical methods for determination and quantification of OLZ in pharmaceutical formulation as well as in biological samples as stated in the literature. Additionally, this review focuses on only the methods reported in the period of 1995- 2018.

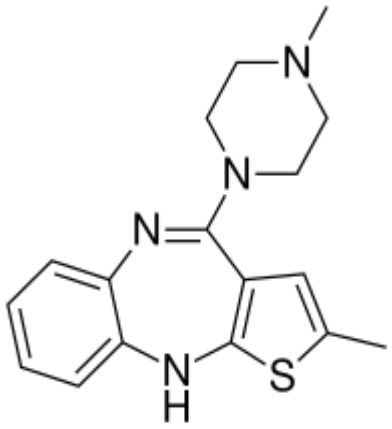

Figure 1. Chemical Structure of OLZ

Metabolites of OLZ

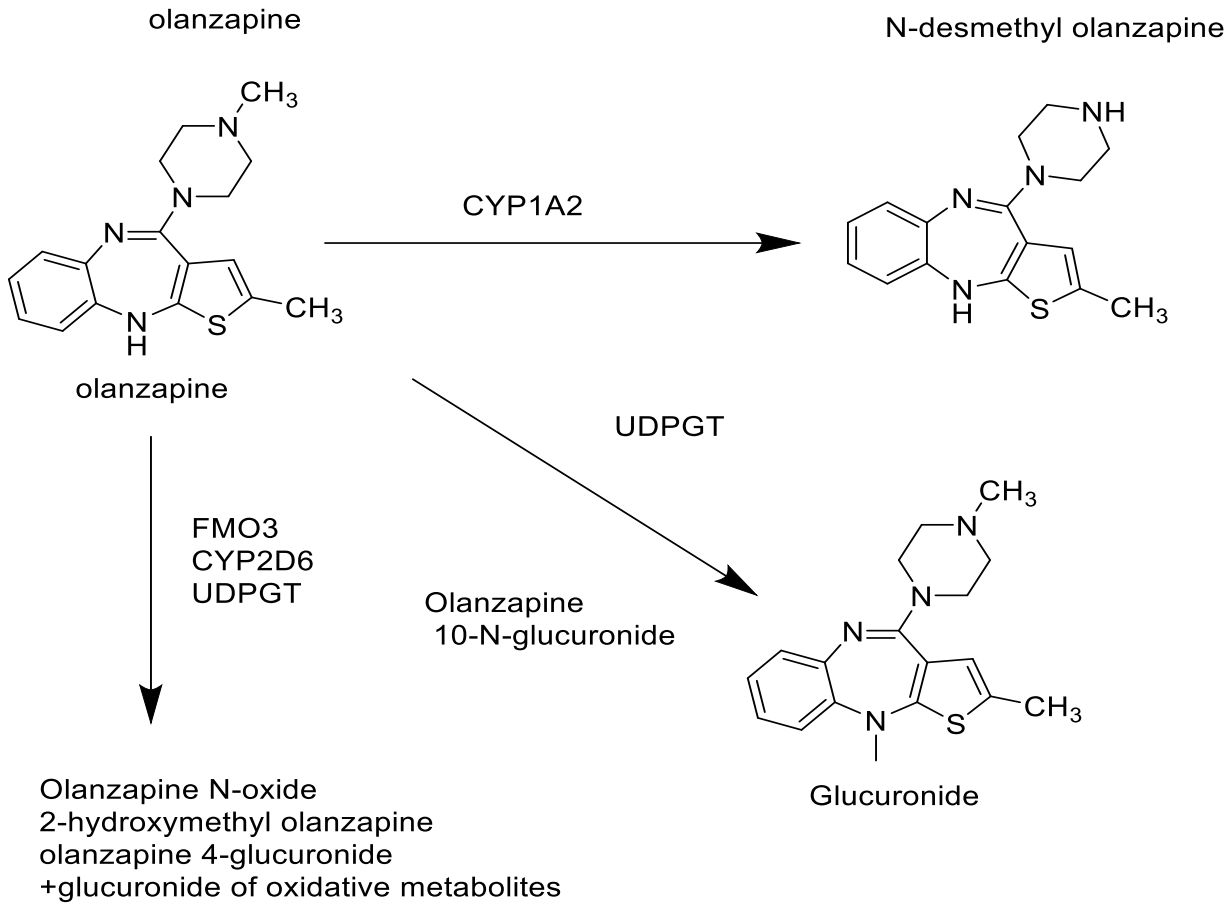

Figure 2. Metabolites of OLZ

Pharmacopoeial status:

OLZ is the official drug in Indian Pharmacopoeia (IP) - 2007, Indian Pharmacopoeia (IP) – 2010, Indian Pharmacopoeia (IP) – 2014, the Merck index Thirteenth edition, the Merck index fourteen editions and Martindale.

IP depicted HPLC assay method using C18 (25 cm × 4.6 mm, 5µm) column as a stationary phase and mobile phase consisted of 3gm of ammonium dihydrogen orthophosphate adjust pH to 2.5, water and triethylamine (70:30 *v/v*) with a flow rate of 1 mL/min. Column effluent was monitored at 220 nm [5].

IP depicted HPLC assay method using C18 (25 cm × 4.6 mm, 5µm) column as a stationary phase and mobile phase consisted of 3gm of ammonium dihydrogen orthophosphate adjust pH to 2.5, water and triethylamine, Methanol (70:30 *v/v*) with a flow rate of 1 mL/min. Column effluent was monitored at 220 nm [6].

IP depicted HPLC assay method using C18 (25 cm × 4.6 mm, 5µm) column as a stationary phase and mobile phase consisted of 4.83gm of sodium dihydrogen orthophosphate monohydrate adjust pH to 6.8, Acetonitrile and Methanol (80:20 *v/v*) with a flow rate of 1.2 mL/min. Column effluent was monitored at 230 nm [7].

BP depicted HPLC assay method using C18 (25 cm × 4.6 mm, 5µm) column as a stationary phase and mobile phase consisted of 0.345%w/v sodium dihydrogen phosphate monohydrate adjusted to pH 6.8 with dilute sodium hydroxide.buffer,Acetonitrile and Methanol (25:75*v/v*) with a flow rate of 2 mL/min. Column effluent was monitored at 250 nm [8].

Analytical Methods for OLZ determination of HPLC Method:

Various separation techniques such HPLC have been employed for the determination of OLZ in pharmaceutical matrix as well as in biological samples. But, HPLC technique was mostly utilized for determination of OLZ. Most of the researchers utilized C18 reverse phase analytical column for separation of OLZ.

Maximum analytical studies with HPLC employed for determination of OLZ in pharmaceutical formulation on C18 reverse phase analytical columns. Water and Methanol in the ratio of 30:70 v/v or 70:30 v/v mixture as a mobile phase, associated or not with some organic additives such as buffers, acids or bases, methanol to improve selectivity and separation. The wavelength was used in HPLC methods ranges from 220-295 nm but in general it was set at 235 nm. The data related to simultaneous determination of drugs was specified in **Table 1 [9-18].**

HPLC Simultaneous method development:

Mahmoud A Tantawy et al. (2012) A spectrophotometry sensitive, accurate, & precise. TLC spectrodensitometry & HPLC method for simultaneous determined for OLZ & FLU-HCl. two spectrophotometry techniques developed first derivative (D1) & derivative ratio (DD1). The precoated aluminium TLC plate with silica gel GF254 Stationary Phase & mobile phase mixture methanol: toluene: ammonia (7:3:0:1v/v/v) chromatogram wavelength at 235 nm.The HPLC developed methods used RP-C18 column with isocratic elution. The mobile phase mixture Acetonitrile: triethylamine (53:47:0.03v/v/v) pH adjusted 4 & flow Rate was found to be about 1.0ml/min. The wavelength at 235 nm. [11].

C. Vitorino et al. (2013) The RP-HPLC method developed by the Simultaneous determinate for SA, prodrug & the respective active hydroxy acid, SA & OZL in dosage form. Containing coencapsulating-Nanostructured lipid carries. The chromatography separation was carried by Phenomenex Luna phenyl-hexyl column, (5µm,150× 3 mm) temperature at 35ºC, & Socratic Conditions Used wavelength at 230 nm.The mobile phase mixture ammonium acetate aqueous solution 0.02M, methanol and Acetonitrile (30:35:35v/v/v) and flow rate was found to be about 0.8ml/min. The linear regression analysis, calibration curve good concentration range was found to be 0.5-100µg/mL, r2=0. 9994 for all three compounds, SA, OLZ. [12].

Table 1. Simultaneous estimation of drugs by HPLC

Sr no	Name of drug/ formulation.	Column	Mobile Phase Composition	Detection (nm) Detector	Linearity Retention Time	Flow rate (ml/min)	Ref
1	OLZ+FLU HCl Tablet	Inertsil C18 ODS column	Acetonitrile: Methanol (90:10V/V)	UV detector **233**	20-80µg/ml 2.7min For Fluoxentine HCl and 3.3min	1	9
2	OLZ + FLU HCl Tablet	C18 column	Acetonitrile: methanol: 0.032 M ammonium acetate buffer (45:05:50V/V/V)	UV/Visible detector **235**	0.2-4µg/ml 0.1-2 µg/ml 300–1000 - 150–500 ng 1.95.min	1.5	10
3	OLZ + FLU Capsule	Zorbax ODS column C18 column	Phosphate buffer pH 4.0:acetonitrile:triethylamine(53:47:0.03V/V/V)	UV detector **235**	20–100 ug/mL. 100–600 ug/mL. 2.74, 9.77min.	1.0	11

4	OLZ +SA	Luna Phenyl Hexyl,c18 column	Ammonium acetate aqueous solution 0.02Mmethanol:Acetonitrile (30:35:35 V/V/V)	UV/visible detector **230**	0.5-100 µg/mL 7 min	0.8	12
5	OLZ+CLZ+QUE Several beta-blockers	RP-4 ADS column	Ethanol : water (80:20 V/V)	PDA Detector **215**	20-80 µg/ml 10.89 min	1	13
6	OLZ+FLU HCl Tablet	C18 column	Acetonitrile: pot. Dihydrogen phosphate buffer: trietythimine (0.2%) (0.1%v/v ortho phosphoric acid PH3.1) (40:60:02V/V/V)	UV detector **233**	10 - 60µg/ml 20-120µg/ml 1.96&1.59min	1.0	14
7	OLZ +FLU Tablet	C18 column	75mM potassium dihydrogen phosphate buffer (pH4.0): Acetonitrile: methanol (55:40:5V/V/V)	UV /visible detector **227**	5–80µg/mL & 20–320 µg/mL	0.8	15
8	OLZ+FLU HCl Tablet	HYPERSIL ODS C18 column	0.01M Phosphate buffer PH 5.8: Acetonitrile (55:45V/V) pH-2.6 adjusted with Orthophosphoric acid)	PDA detector **261**	18-42µg/ml and 72-168µg/ml. 3.480 and 2.597 min	1	16
9	OLZ+FLU HCl Tablet	C8 column	0.1%v/v Ortho Phosphoric acid in water (pH 3.5 With Triethylamine):Acetonitrile: Methanol (60:30:10V/V/V)	PDA detector **225**	12-28µg/ml 48-112µg/ml 2.19 min and 3.71.	1.0	17
10	OLZ Tablet	Inertsil C18 column	9.5 mM sodium dihydrogen phosphate (pH adjusted to 6.8 ± 0.1 with triethylamine) : Acetonitrile : methanol (40:30:30 V/V/V)	PDA detector **225**	25 -75 µg/mL 100–300 µg/mL 10 min	1.2	18

HPLC method indicating stability study, impurity profiling methods

Ramisetti Nageswara Rao et al. (2008) The simultaneous determination of OLZ by RP- HPLC method. A process impurity in bulk drug & tablet dosage form was developed. The separation was accomplished on Inertsil ODS 3V column (4.6mm, 250mm, 5µm). The mobile phase mixture of 0.2M ammonium acetate (pH= 4. 50): ACN in gradient elution mode. The analysis was PDA detector wavelength at 254 nm. The flow rate was found to be 1.0ml/min. [21].

Table 2. HPLC method indicating stability study, impurity profiling for OLZ

Sr no	**Name of drug/ formulation.**	**Column**	**Mobile Phase Composition**	**Detection (nm) Detector**	**Linearity Retention Time**	**Flow rate (ml/min)**	**Ref**

11	OLZ Bulk	Inertsil C18 column	Ammonium phosphate buffer : methanol (70:30 v/v)	UV-Visible detector SPD 10 **220**	2 - 10µg/ml 3.447min	1	19
12	OLZ+CMZP Tablet	ACE5–CN column	Phosphate buffer (pH 5.0 25 mM) : methanol (80:20 v/v) (70:30 v/v)	UV/DAD detector **254**	0.2–50.0 mg/mL	1	20
13	OLZ Tablet	Inertsil ODS 3V column	Water: methanol (30:70v/v).	PDA detector **254**	10 - 300 µg/mL	1.0	21
14	OLZ Tablet	Intersil ODS column	Ammonium acetate (pH4.5):Acetonitrile (70:30v/v)	PDA detector UV detector **271**	10-200 mg/mL 7.48 min	0.5	22
15	OLZ Tablet	C18 column	Potassium dihydrogen phosphate Buffer (pH 6):Acetonitrile (60:40) (v/v)	UV detector **258**	5-25 µg/ml 5 min	1	23
16	OLZ +PAL Bulk	C18, YMC packpro C18, Inertsil ODS 3V	0.1%Ammonium Acetate in water : Acetonitrile (95:5 v/v)	PDA detector **254**	0.2 mg/ml and 0.5mg/ml 0.2 mg/ml and 0.5 mg/ml	0.8	24
17	OLZ Bulk	Agilent Octyldecyl silica column (TC-C18,	Methanol: 0.3% TEA in water (36 : 64 v/v)	UV/Visible detector **254**	50 mg ml - 320 mg/ml 11.10 time /min	1.0	25
18	OLZ Tablets	Kromasil C-18 column	Acetonitrile: phosphate buffer (30 : 70 v/v)	DAD **258**	10 - 50 µg /mL 1.850 min	1.5	26
19	OLZ Tablet	BDS Hypersil C18 Column	0.01M Tetra butyl ammonium hydrogen sulphate: Methanol (60:40 v/v).	UV Detector **228**	10-80µg/ml 10.0 min.	1.0	27
20	OLZ Bulk and Tablet	Intersil ODS 3V column	10mM disodium hydrogen phosphate buffer (pH 7.4) : Acetonitrile (35 :	UV/ visible detector **254**	2.5–20.0 µg/mL 4.39 ± 0.01min	1.0	28

			65v/v)				
21	OLZ Tablet	ODS A-132 C18 column	phosphate buffer (pH: 5.5): Acetonitrile (7:3 v/v)	DAD **295**	1.61×106 - 7.24×104 min	1.3	29

Bio-analytical Method:

The Bioanalytical Method development in Table 3

Christoph Hiemke et al. (2001) A simultaneous technique of the antipsychotic drug CLZ, OLZ, & demethylated metabolites. Method included adsorption CPS coated clean up column washes & interfering serum constituents to waste separation on ODS Hypersil C18 column RP- material (5 µm, 250 × 4.6 mm). A used mobile phase mixture of Acetonitrile: water: tetra methyl ethylene diamine (37:62.6.4v/v/v) pH adjusted 6.5 concentrated acetic acid. The UV detection Lamda max at 254 nm. The LOQ was found to be 10-20ng/ml. Relative standard variation ranges between 4.5 and 13.5 [33].

Huande Li et al. (2012) sensitive, rapid LC-MS/MS technique coupled with column developed for the determined of OLZ in rat brain microdialysates. The both columns C8 guard column used samples before analysis separate on a C18 column & detection with tandem mass spectrometry. The both mobile phase mixtures of methanol: Acetonitrile: water (43:43:14v/v/v) was for analysis separated, water in both mobile phases contained 0.1% ammonium acetate. The LOQ for OLZ was found to be 0.085ng/ml. The linear from LOQ to 34ng/ml with a coefficient of determination more than 0.998. Precision study Intraday and interday& accuracy were determined with variability less than 13.24% (RSD). [35].

M. a. raggi et al. (2001) The HPLC method with electrochemical detection has been developed for the determination of olanzapine and its main metabolite, desmethylolanzapine, in human plasma. Chromatographies separation and analysis was performed on a C8 reversed phase column with a mixture of methanol, Acetonitrile, and pH 3.7 phosphate buffer as mobile phase, 2-methylolanzapine was used as internal standard. The response was linearly dependent on concentration and precision were satisfactory over the concentration range 0.5-75.0ng/ml for both analytes. The limit of detection was 0.2ng/ml for both analytes. [36].

Table 3. Bioanalytical paper

Sr no	**Name of drug**	**Sample matrix**	**Column**	**Mobile phase composition**	**Detection (nm) detector**	**Flow rate (ml/min)**	**Ref**	**Internal standard**
1	OLZ+ RIS+ 9-HYD RIS	Human Plasma	RP18 column	10 mM ammonium acetate buffer at a pH of 3.5 which was adjusted with acetic acid : Acetonitrile (70:30v/v)	PDA detector **277**	0.3	30	Clozapine
2	OLZ	Human Plasma	YMC column	75 mM sodium phosphate (pH 7) : methanol: Acetonitrile (48:26:26 v/v/v).	Electrochemical detection	1.2	31	Olanzapine
3	OLZ	Rat Plasma	column C18hypersil-BDS	50 mM phosphate buffer pH 5.5: Acetonitrile : methanol	UV detector **214**	1.2	32	Olanzapine

				(50:30:20 v/v/v)				
4	OLZ	Human Breast Milk	YMC basic column	75mM phosphate buffer pH 7.0: acetonitrile : methanol (48:26:26v/v/v)	Electrochemical detection	1	33	Olanzapine
5	OLZ	Serum	Normal-phase silica gel column	50 mM ammonium acetate buffer adjusted to pH 9.9 with ammonia water: methanol (15:85v/v).	UV detector **270**	1.1	34	Trifluoperazine
6	OLZ+CLZ	Serum	C18 ODS Hypersil	Acetonitrile : water tetramethyl ethylene diamine(37:62.6:0.4 v/v/v)	UV detector **254**	1.5	35	Olanzapine and demethylolanzapine.
7	OLZ+CLZ +RISPQUT	Rat Brain	Macherey nagel C18 column	water (formic acid: 2.70 mmol/l ammonium acetate: 10 mmol/l) : Acetonitrile (53:47v/v)	UV detector **254**	0.16	36	Olanzapine and quetiapine
8	OLZ	Human plasma	C18 column	0.06 M ammonium acetate buffer pH 5.9 : Acetonitrile : methanol (40: 41 :3 : 7 v/v/v)	electrochemical detector	0.69	37	Clozapine
9	OLZ	Human plasma and Urine	Supelcosil LC-CN column	10%methanol25% acetonitrile and 65% 50 mM phosphate buffer pH 6.0	UV detector **214**	1	38	Olanzapine
10	OLZ	Rat plasma	YMC basic column	75mM phosphate buffer (adjusted to pH 7 with 5 M Sodium hydroxide) : Acetonitrile : methanol (48:26:26 v/v/v)	electrochemical detector	1.2	39	Olanzapine

11	OLZ	Human Plasma	Spherisorb S5 C6 analytical column	Water : Acetonitrile (55:45 v/v)	UV-VIS detector **254**	1.0	40	Clozapine
12	OLZ	Human Plasma	C 18 column	14% acetonitrile in water (containing 0.25% H PO and 0.05% triethylamine)	electrochemical detectors **270**	1	41	N-desmethyl clozapine
13	OLZ+DESMOLZ	Human Plasma	C8 column	Methanol(11%o),acetonitrile(9.7%), and 8.9mmol L 1 phosphate buffer(79.3%)containing 7.18mmolL 1 Triethylamine	Decade amperometric detectors **316**	0.7	42	Methylolanzapine
14	OLZ	Human Plasma	column C8	Acetonitrile:13.5m M, pH 2.0 phosphate buffer (30:70 v/v pH = 2.5)	UV detector **260**	1	43	Tripralidine
15	OLZ+ARI	Human plasma	column Rp-18	Phosphate buffer (pH 3.14, 20 mM) and acetonitrile	Diode array detector. **255**	0.8	44	Carbamazepine

Spectrophotometric method:

Spectrophotometric methods with UV-Visible detection have been developed for OLZ analysis without combination illustrated in Table 4, 5, 6 [45-62].

Kishanta Kumar Pradhan et al. (2014) The Olanzapine in pure and tablet form. The simple, specific and reliable UV-VIS spectrophotometry method was studied. The bulk forms mobile phase mixture of water: hydrochloric acid (9:1). The Lamda max at 258 nm. The regression equation and calibration graph, respectively. The concentration range of 5-40µg/ml. The correlation coefficient was found = 0.059x + 0.171 and 0.998 respectively [45].

S.firdous et al. (2005) The determination of olanzapine, based on UV spectrophotometry new method and non- aqueous titration, has been developed. The Lamda max at 226 nm. In a methanolic solution of olanzapine. The concentration range was found to be 0.1g/ml to 50g/ml beers law obeys and interday precision of UV is 0.97%. The non-aqueous titration was carried by olanzapine with 0.1N Perchloricacid. Using naphthobenzene as indicators and Intraday precision ranges 0.35%. [50].

Sahar R. Fadhel et al. (2016) The new spectrophotometric techniques have been developed for the assay of olanzapine in bulk and tablet forms. This both methods, in acidic medium based on the diazocouping of olanzapine and diazotized p-Nitroaniline to form a stable brown colored water-soluble azo dye. The maximum Lamda max at 405 nm. The concentration linear range was found to be 0.5-45.0 µg/ml. 1.5777×104 L. Mol-1. Cm the LOD was found to be 0.3148 µg. mL-1 and sandals sensitivity values were found to be 0.0198 µg/cm. [53].

Table 4. UV- Spectroscopy method

Sr.no	Drug	Method Wavelength (nm)	Matrix	Linearity/lod/loq	Ref
1	OLZ	UV Spectroscopic Method **258**	Bulk	5-40µg/ml LOD=0.4306ug/ml LOQ=1.305ug/ml	45
2	OLZ	Spectrophotometric methods **410 ,620**	Balk Formulation Using Bromocresol Green	0.25-12.5µg/ml and 0.2-5.0ug/ml LOD=0.28and 0.03ug/ml LOQ=0.86 and 0.08ug/ml	46
3	OLZ	UV Spectrophotometric Methods **258 ,252**	Bulk	3-18 µg/ml and 4-24 µg/ml LOD=0.1680and 0.2018ug/ml LOQ=0.5091and 0.6115ug/ml	47
4	OLZ	Spectrophotometry Methods **550, 610**	Tablets	2.0 -20µg/ml and 1.0- 10 µg mL LOD and LOQ=0.37 and 1.13 µg mL 0.16 And 0.48 µg mL-1.	48
5	OLZ	UV Spectrophotometric method **270, 304 & 304**	Tablets	10-16 µg/ml LOD=0.101, 0.209,0.109ug/ml LOQ=0.306, 0.634,0.332ug/ml	49
6	OLZ	UV Spectrophotometry and non-aqueous titration **226**	Tablet	0.1 - 50ug/ml 0.2 - 100mg/m LOD=0.1ug/ml,0.3mg	50
7	OLZ	Spectrophotometric methods **222, 230**	Bulk	*2*-10 µg/ml LOD=500ug/ml & 499ug/ml LOQ=166.6ug/ml & 159.2ug/ml	51
8	OLZ	Highly sensitive Spectrophotometric method **610**	Bulk	0.3 - 8.0ug/ml LOD=0.1290ug/ml LOQ=0.3696ug/ml	52
9	OLZ	Spectrophotometric method **405**	Bulk	0.4 – 45ug/ml LOD=0.3148ug/ml LOQ=1.0495ug/ml	53

Simultaneous method development

Farzana I Ghanchivhora et al. (2017) The spectrophotometry techniques simple, specific, accurate, precise and economical has been developed for the both drug olanzapine and paliperidone in synthetic mixture. The olanzapine maximum Lamda max at 259 NM & paliperidone maximum Lamda max at 269 nm. The concentration liner range of olanzapine 2-12 µg/ml and paliperidone range 3-18 µg/ml [57].

Table 5. Simultaneous UV- Spectroscopy method

Sr. no	Drug	Method Wavelength (nm)	Matrix	Linearity Lod/Loq	Ref
10	OLZ+FLU HCl	Simultaneous Methods **318,239**	Bulk	10 - 60 mg/ml LOQ= 0.73 to 1.49 mg/ ml and 0.18 to 0.96 mg/ ml	54
11	OLZ+CLOZ+ QUES+several beta-blockers	Simultaneous Methods **215, 226, 242 and 299**.	Tablet	20-80 µg/ml LOQ=2.5µg/ml LOD=2.50 µg/ml	55
12	OLZ+FLU HCl	Simultaneous method **226,258**	Bulk	10-100 µg/ml 10-100 µg/ml LOD=1-10 µg/ml LOQ=10-50 µg/ml	56
13	OLZ+ PAL	Simultaneous method **269, 259**	Bulk	3-18 µg/ml and 2-12 µg/ml LOD=0.2131 0.645µg/ml LOQ=0.218 0.662µg/ml	57

Analysis with combination drug

HD Revanasiddappa et al. (2012) The spectrophotometry method simple, sensitivity determined by OLZ &ORPDN bulk dosage form. The method developed is based on the ternary complex formulation of drugs under investigation with Essen and lead (II) by using methyl cellulose as a surfactant. The maximum wavelength at 540 nm both drug OLZ & ORPDN. The optimum experimental conditions for the ternary complex formulation established. The both methods obeys bees law concentration range was found to be 0.0-35.0 and 0.0-55 µg/ml. [58].

Table 6. UV – Spectroscopy with combination drug

Sr.no	Drug	Method Wavelength (nm)	Matrix	Linearity/lod/loq	Ref
14	OLZ +ORPHE	Sensitive Spectrophotometric Method **540**	Bulk	0.0-35.0µg/ml and 0.0-55 µg/mL LOD=0.4547 and 0.9422µg/ml LOQ= 0.1501 and 0.3109 µg/ml	58
15	OLZ+ 1,2 NAPTHOQUI -4 SUL (NQS)	Spectrophotometric method **454**	Tablet	0.4 - 4.0µg/ml LOD=0.09µg/ml LOQ=0.29µg/ml	59
16	OLZ +P-DIMETHYL AMINO BENZ	Spectrophotometric method **410**	Bulk	5–160µg/ml LOD=6.6µg/ml LOQ=20µg/ml	60
17	OLZ +CER (IV) SUL	Visible Spectrophotometry **480, 640, 700**	Tablets	0.2-2.0µg/ml0.5-9.0µg/ml 0.2- 3.0µg/ml LOD=0.01, 0.04, 0.01µg/ml LOQ=0.02, 0.11, 0.03µg/ml	61
18	OLZ+ N BROMO SUSSIMIDE +CERB(IV)SUL	Spectrophotometric method **532, 538 ,538**	Bulk	10 – 120µg/ml 0.5 – 6.0µg/ml 0.6 – 3.0µg/ml LOD=2.10ug/ml 0.10µg/ml 0.16µg/ml LOQ=6.99µg/ml 0.30µg/ml 0.37µg/ml	62

High-performance thin layer chromatography (HPTLC):

The HPTLC technique overcomes the limits of TLC as well as takes advantage over the HPLC techniques. It shows the advantages like less time consuming,

cheap, utilizes disposable stationary phases, less sample required compared to TLC, gives static and offline detection ability and high throughput qualitative and quantitative detection. The analytical information about HPTLC illustrated in **Table 7 [63-66].**

Sejal Patel et al. (2009) The two different techniques a binary mixture of fluoxentine Hcl and olanzapine. The first method RP-HPLC determined of fluoxentine Hcl and olanzapine. The mobile phase mixture of Acetonitrile: methanol: 0.032 M ammonium acetate buffer (45:05:50, v/v/v). The flow rate was found to be 1.5ml/min. Lambda max at 235 nm. The concentration range was found to be 0.2-4µg/ml and 0.1-2µg/ml. The both drug % recovery was found to be 101.16±0.59 and 99.79±0.56%. The second method HPTLC the both drugs, separation followed by densitometry measured of their spots at 235nm. The separation carried out by Merck TLC aluminium plate of silica gel 60F254. The mobile phase mixture of acetone: methanol: triethyleamine (5:3:0:5v/v/v). The linearity was found to be in the range of 300-1000ng/spot and 150-500ng/spot and % recovery were found to be 100.95±0.52 and 99.31±0.51% for Fluoxetine HCl and olanzapine. [65].

Table 7. HPTLC determination of OLZ

Sr no	Drug	Formulation	Stationary Phase Plate	Mobile Phase Composition	Detection in (nm)	linearity	Rf	Ref
1	OLZ+ FLU	Tablet	Silica gel 60F254	Methanol: toluene (4:2v/v)	**233**	100-800 ng/spot 1000-8000 ng/spot	0.31±0 .01	63
2	OLZ+ DUOH Cl Synthetic Mixture	Capsule	Silica gel 60 F254	Toluene: methanol:10% ammonia3:1.3:0 .05 (v/v)acetone: methanol: triethylamine(5: 3:0.5v/v/v)	**231, 240**	60–480 ng/spot per 100-800& 50–400 ng	0.39 ±0.02 0.63 ±0.02 & 0.77 ± 0.02,	64
3	OLZ+ FLU HCl	Tablet	Silica gel 60 F254	Acetone:methanol:triethyleamine (5:3:0.5 v/v/v)	**235**	300–1000 & 150–500 ng/spot	_	65
4	OLZ	Bulk	Silica gel 60F254	Methanol :ethyl acetate (8.0 + 2.0 v/v)	**285**	100 - 600 ng/band	Rf = 0.35 - 0.02	66

LC-MS/MS method:

Coupling of HPLC with single MS or MS–MS is highly sensitive, able to analyze multicomponent, to inspect the specificity of the analysis and most reliable method to evaluate active ingredients from biological samples. In existing LC/MS/MS techniques, ionization of the sample is carried out under atmospheric pressure (atmospheric pressure ionization (API) which is separated from the high vacuum portion of the mass analyzer. Two commonly

used methods of atmospheric pressure ionization involve electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI) of the molecules to be analyzed. The most use mobile phase was 10mM aqueous ammonium acetate adjusted to pH 4 with formic acid and Acetonitrile along with methanol. And for analysis of sample generally used matrix was Human plasma. The mass to charge ratio was used in the range of 313.2-256.3 and extraction of samples done by various methods such as protein precipitation, liquid-liquid extraction, solid-liquid extraction, Serum or cerebral spinal fluid samples, ion-exchange cartridges, Rat brain homogenate and analyzed etc. The separation was carried out on the C18 column generally. The concise analytical data related to the LC-MS/MS is depicted in **Table 8 [67-82].**

Michael G. Bartlett et al. (2007) The analytical method extract from rat brain homogenate and analyzed by LC-MS/MS. sample prepared and chromatography study, he method used a Water Atlantis TM dC-18 column (30mm×2.1mm 3mm). Gradient elution the mobile phase mixture of Acetonitrile: 5mM ammonium Formate adjusted pH6.1 with formic acid. The analytical method in positive ion separated used multiple reaction monitoring. [68].

Table 8. LC-MS

Sr. no	Drug	Matrix	Extraction method	m/z ratio		LC Separation	Lod/Loq	Ref
					Column	M.P		
1	OLZ	Human Plasma	solid phase extraction	m/z 313/256 m/z 384/253	ACE5 C18-300 column	(5:95,10:90,15:85,20:80 and 30:70v/v) of water methanol: Acetonitrile : formic acid : ammonia(0.010.005%) ammonium trifluoroacetate ammonium acetate or ammonium formate buffer sin varying strengths (2–20mM)	LOD=0.10&0.012 ng/mL	67
2	OLZ+RISP,9 HYDRORISP+ CLOZ+ HOPO +ZIPRAS	Rat Brain Tissue	Rat brain homogenae and analyzed	m/z 313m/z 256 32V 23 eV	C8 guard column.	100µl of methanol: 20mM ammonium formate (pH3.86, adjusted by formic acid) (70:30v/v).	LOQ=0.208 ng/ml	68
3	OLZ	Human Blood	Liquid–liquid extraction	(*m/z*313.4256.2)*327.3 270.1)*	Monochrm HPLC column	100 mM ammonium acetate: methanol: isopropanol: water (15:4:1v/v/v).	–	69
4	OLZ+FLU	Human Plasma	Plasma samples on Waters	m/z 313, 310, 316and 315	Themo Hypersil Gold C18	2 mM ammonium acetate: Methanol (10:90 v/v)	LOQ=0.50 ng/ml	70

5	OLZ	Rabbit Plasma	Liquid-Liquid extraction	m/z 313.4 →256.3	C18 column	0.1% v/v formic acid in water : Methanol (08:92 v/v)	LOQ=5ng/ml	71
6	OLZ+FLU	Human Plasma	Solid phase extract on	m/z 310.01!147.69 313.15!256.14 298.1!153.97	Gold C18column	Acetonitrile: water containing 2% formic acid (70:30v/v)	LOQ=0.37 ng/ml	72
7	OLZ	Human Plasma	Liquid–liquid and SPE extraction	m/z 313.3 → 256.1	YMC-ODS-AQ C18 Column	10 mM ammonium acetate in water contained 0.05% (v/v) formic acid (pH 3.5) methanol containing 0.05% (v/v) formic	LOQ=0.2 ng/ml	73
8	OLZ	Human Plasma	Liquid- liquid extraction	m/z 313.15	ZORBAXEclipse XDB-CN column	Acetonitrile : aqueous ammonium acetate solution (pH 4.0, 10 mM) (56:44v/v)	LOQ=0.5ng/mL	74
9	OLZ	Blood	Solid-phase extraction	m/z 313 → 256 m/z 313 → 84	Revered phase Zorbx Extend-C18column	Methanol : Acetonitrile : ammonium hydroxide (25:25:50 : 5 mM v/v/v)	LOQ=0.005mg/kg	75
10	OLZ+RISP+QUE+CLOZ+ZIPRAS+PERO+ ARIPI	Human Serum	Solid-phase extraction	–	Mightysil-RP-18 MS column	10 mM formic ammonium buffer (pH 6.0) : Acetonitrile	LOD=0.00071, 0.031, 0.015, 0.046, 0.017, 0.0057, 0.012 and 0.027ng/ml LOQ=20ng/ml	76
11	OLZ+N-DESMETHYL OLZ	Human Serum and Cerebrospinal Fluid	Serum or cerebral spinal fluid samples	–	Hydro-RP column	buffer (10mM 0.05% formic acid dilution of 5ml ammonium formate stock Solution and 250ml formic acid (98%)	LOQ=0.3 ng/ml& 0.9 ng/ml	77

12	OLZ+DESMETHYL OLZ	Anticoagulant and lipemia	Waters Oasis MCX cartridges and analyzed	m/z 312.9/256.0	Phenomenex LUNA pheyl hexyl,column	Acetonitrile: ammonium acetate (20 mM) (52:48v/v). Formic acid : Acetonitrile (0.1:100 v/v).	–	78
13	OLZ	Human Urine	Solid-phase extraction	–	C18 column	Ammonium acetate (pH 7.8): Acetonitrile (10:90v/v).	LOQ= 1ng/ml	79
14	OLZ	Human Plasma	Liquid–liquid extraction.	m/z: 313.1 > 256.1 278.1 > 260.2	ACE C18, column	water with 0.1% formic acid Acetonitrile : 0.1% formic acid (50 : 50 v/v)	LOQ= 1ng/ml	80
15	OLZ+FLU+NOR FLU	Human plasma	Liquid-liquid extraction	m/z 313.10 →256.05, m/z 310.10 →148.00, m/z 296.05 →133.90	Agilent Eclipse Plus C18 column	Methanol: 20 mM ammonium formate buffer (82.5: 17.5 v/v).	LOQ=0.05 ng/ml	81
16	OLZ	Human plasma	Liquid–liquid extraction	m/z 313/256	Revere phase C18 column	10mM ammonium acetate buffer : Acetonitrile (10:90v/v)	LOQ= 100 pg/ml	82

CONCLUSION:

The present review illustrates various analytical approaches executed for the valuation of OLZ. An abundant investigation had performed, including, HPLC, Bio-analytical, HPTLC, UV/Vis-Spectroscopy, LC-MS/MS, GC-MS, etc. for estimation of OLZ in bulk and in its combined pharmaceutical formulations and in plasma. High performance-Liquid chromatography with UV detection has been found to be the most studied for estimation of OLZ in bulk as well as pharmaceutical formulations, while hyphenated LS-MS/MS method was reported for determination of OLZ and its metabolite in plasma and other biological fluids. Further, methods were reported for its pharmacokinetics as well as bioequivalence studies. Few chromatography approaches like HPTLC and Stability-indicating HPLC analysis is also reported in the literature. Certain Spectrophometric methods in UV-Visible spectroscopy analysis is most often used for assessment for OLZ.

Acknowledgements:

Authors are thankful to R.C. Patel Institute of Pharmaceutical Education and Research Shirpur,

Dist.: Dhule (MS) 425 405 for providing necessary library facilities.

Conflict Of Interest:
Authors do not have conflict of interest for this manuscript.

Abbreviations:

- OLZ - Olanzapine
- FLU- Fluoxetine
- CLZ- Clozapine
- CMZP- Carbamazepine
- PAL- Paliperidone
- RIS- Risperidone
- ARI- Aripiprazole
- ORPHE- Orphenadrine
- SA- Simvastatin
- LC-ES/MS/MS- Liquid chromatography Electrospray-mass spectroscopy-mass spectroscopy
- GC-MS-MS- Gas chromatography- mass spectroscopy-mass spectroscopy
- LC-MS- Liquid chromatography-mass spectroscopy
- SEM- Simultaneous equation method
- RF- Retention factor
- ESI- Electro-spray ionization
- nm-Nanometer
- M.P.- Melting point
- ACM-Absorption correction method
- ACN- Acetonitrile
- FA- Formic acid
- MFE- Mercury film electrode
- HMDE- Hanging mercury drop electrode
- CZE- Capillary zone electrophoretic
- MEKC- Micellar electro kinetic capillary chromatographic

REFERENCES:

1. The Merck Index an Encyclopaedia of chemicals. (2001). Drugs, and biological. Merck Research Laboratories, Whitehouse station. 13th Edition, New Jersey, pp. 6889.
2. The Merck Index an Encyclopaedia of chemicals. (2001). Drugs, and biological. Merck Research Laboratories, Whitehouse station. 14th Edition, New Jersey, USA pp. 6826.
3. Martindale. (2005). the Complete Drug Reference, 34th Edition, Pharmaceutical Press, pp. 696.
4. The Merck Manual of diagnosis and therapy. (1999). Published by Merck research laboratories division of Merck & co.Inc, Whitehouse station. 17th Edition, New Jersey, pp. 1570.
5. Pharmacopoeia-Volume III. I (2007). Published by Indian Pharmacopoeial Commission for Ministry of Health and Family Welfare, Ghaziabad 1681, pp. 156, 358, 1471-1472.
6. Pharmacopoeia-Volume III. (2010). Published by Indian Pharmacopoeial Commission for Ministry of Health and Family Welfare, Ghaziabad, pp.163, 388, 1811-1812.
7. Pharmacopoeia-Volume III. I (2014). Published by Indian Pharmacopoeial Commission for Ministry of Health and Family Welfare, Ghaziabad, pp. 193, 527, 2370-2372.
8. British Pharmacopoeia Commission, General Medical Council (Great Britain) and Great Britain. Medicines Commission. (2001). British pharmacopoeia (Vol. 1). Her Majesty's Stationery Office, pp. 6490.
9. Shahina, S. K., Gobinath, M., Haribaskar, V., Dhani, R. (2015). Analytical Method Development and Validation by RP-HPLC for Simultaneous Estimation of Fluoxetine Hcl and Olanzapine in Combined Tablet Dosage Form. *IJMPR*, 3(5), 1198–1206.
10. Patel, S., & Patel, N., J. (2009). Simultaneous RP-HPLC and HPTLC estimation of Fluoxetine hydrochloride and olanzapine in tablet dosage forms. *Indian journal of pharmaceutical sciences*, 71(4), 477-480.
11. Tantawy, M. A., Hassan, N., Y., Elragehy, N., A., & Abdelkawy, M. (2013). Simultaneous determination of olanzapine and Fluoxetine hydrochloride in capsules by spectrophotometry, TLC-spectrodensitometry and HPLC. *Journal of advanced research*, 4(2), 173-180.
12. Vitorino, C., Sousa, J. J., & Pais, A. A. C., C. (2013). A rapid reversed-phase HPLC method for the simultaneous analysis of olanzapine and simvastatin in dual nanostructure lipid carriers. *Analytical Methods*, 5(19), 5058-5064.
13. Gracia, S., M., Köppl, A., Unholzer, S., & Haen, E. (2017). Development and validation of an HPLC-UV method for the simultaneous determination of the antipsychotics Clozapine, olanzapine and quetiapine, several beta-blockers and their metabolites. *Biomedical Chromatography*, 31(10), 3968.
14. Eswarudu, M. M., Anitha, M., Gayathri, N., & Chaithanya, T. (2012). A validated RP-HPLC method for the simultaneous estimation of Fluoxetine hydrochloride and olanzapine in pharmaceutical dosage form. *International Research Journal Pharmaceutical*, 3 (4) 310-313.
15. Pathak, A., & Rajput, S., J. (2009). Development of a stability-indicating HPLC method for simultaneous determination of olanzapine and

Fluoxetine in combined dosage forms. *Journal of chromatographic science*, 47(7), 605-611.
16. Pranitha, V. S., Uma M. R., V, Ajitha, A. (2014). Rp-hplc method development and validation for simultaneous estimation of olanzapine and Fluoxetine in tablet dosage Form. *International journal of pharmaceutical research & analysis*, 4 (4) 281-284.
17. Ramachandran, D., Reddy, D., M., & Rao, P., P. (2014). Method development and validation for the simultaneous estimation of Hydrochlorothiazide and Irbesartan in a pharmaceutical formulation by RP-HPLC method. *International Journal of Research in Pharmaceutical and Nano science*, 3(5), 482-490.
18. J., V., L., N., Seshagiri Rao & N., usha rani, (2010). Determination of olanzapine in tablets by hplc. International journal. Chemical. Sciences. 8(4), 2168-2172.
19. Prameela, R., A., & Bala, S., C. (2009). Development of HPLC method for the determination of olanzapine in bulk and dosage forms. *International Journal Pharmaceutical. Technical. Research*, 1, 654-657.
20. Renkoğlu, P., Çelebier, M., & Arıca-Yegin, B. (2015). HPLC determination of olanzapine and Carbamazepine in their nicotinamide co crystals and investigation of the dissolution profiles of co crystal tablet formulations. *Pharmaceutical development and technology*, 20(3), 380-384.
21. Rao, R., N., Raju, A., N., Narsimha, R., & Babu, G., R. (2008). Isolation and characterization of process related impurities of olanzapine using HPLC and ESI-MS/MS. *Journal of separation science*, 31(1), 107-118.
22. Basavaiah, K., & Tharpa, K. (2008). Quantitative determination of olanzapine in pharmaceutical preparations by HPLC. *Journal of the Mexican Chemical Society*, 52(2), 120-124.
23. Jain, N., Joshi, A., Vyas, N., Malviya, S., & Kharia, A. (2017). Development and validation of Rp-hplc method for the estimation of olanzapine in marketed formulation, *Journal of Drug Delivery & Therapeutics.* 7 (7) 121-122.
24. Gadekar, V., Rokde, M, M. (2017). Isocratic reversed-phase hplc method with pda detector for the assay and purity evaluation of olanzapine & paliperidone in bulk drug. *International conference on emanations in modern technology and engineering*, 5 (3) 2321-8169 38 – 39
25. Cui, D., Li, Y., Lian, M., Yang, F., & Meng, Q. (2011). Development of a simple and stability-indicating RP-HPLC method for determining olanzapine and related impurities generated in the preparative process. *Analyst*, 136 (15), 3149-3156.
26. Xia, X., J., & Tao, Z., H. (2004). Determination of olanzapine and its tablets by HPLC. *Chinese Journal of Pharmaceuticals*, 35 (1), 46-48.
27. Murthy1, A., R., Raghu, K., Babu1, Vekariya, N., A. (2015). Analytical method development and validation of olanzapine by high performance liquid chromatography. *International journal of pharmaceutical sciences and drug research, 7 (2) 188-192.*
28. Basavaiah, K., Rajendraprasad, N., & Vinay, K., B. (2014). Isocratic high-performance liquid chromatographic assay of olanzapine: method development and validation. *ISRN Analytical Chemistry*, 1-6.
29. Bıryol, İ., & Erk, N. (2003). Voltammetric, spectrophotometric and high performance liquid chromatographic analysis of olanzapine. *Analytical letters*, 36 (11), 2497-2513
30. Siva, S. K, M., & Ramanathan, M. (2016). Concurrent determination of olanzapine, risperidone and 9-hydroxyrisperidone in human plasma by ultra performance liquid chromatography with diode array detection method: application to pharmacokinetic study. *Biomedical Chromatography*, 30 (2) 263-268.
31. Catlow, J., T., Barton, R., D., Clements, M., Gillespie, T., A., Goodwin, M., & Swanson, S., P. (1995). Analysis of olanzapine in human plasma utilizing reversed-phase high-performance liquid chromatography with electrochemical detection. *Journal of Chromatography B: Biomedical Sciences and Applications*, 668(1), 85-90.
32. Pervaiz, F., Ahmad, M., Minhas, M., U., & Sohail, M. (2015). Development and validation of reverse phase high performance chromatography method for determination of olanzapine in microsample rat plasma: application to preclinical pharmacokinetic study. *Tropical Journal of Pharmaceutical Research*, 14(1), 141-147.
33. Kasper, S., C., Mattiuz, E., L., Swanson, S., P., Chiu, J., A., Johnson, J., T. & Garner, C., O. (1999). Determination of olanzapine in human breast milk by high-performance liquid chromatography with electrochemical detection. *Journal of Chromatography B: Biomedical Sciences and Applications*, 726 (1-2), 203-209.
34. Olesen, O., V., & Linnet, K. (1998). Determination of olanzapine in serum by high-performance liquid chromatography using ultraviolet detection considering the easy oxidability of the compound and the presence of other psychotropic drugs. *Journal of*

Chromatography B: Biomedical Sciences and Applications, 714(2) 309-315.

35. Weigmann, H., Härtter, S., Maehrlein, S., Kiefer, W., Krämer, G., Dannhardt, G., & Hiemke, C. (2001). Simultaneous determination of olanzapine, Clozapine and demethylated metabolites in serum by on-line column-switching high-performance liquid chromatography. *Journal of Chromatography B: Biomedical Sciences and Applications*, 759(1), 63-71.
36. Zheng, Q., Wang, F., Li., H., Xu, P., Tang, H., Li, L., & Cheng, R. (2012). Quantitative analysis of olanzapine in rat brain microdialysates by HPLC–MS/MS coupled with column-switching technique. *Journal of Chromatography B*, 905, 127-132.
37. Kamila, K., S., katarzyna M., Bua and M., B., -k. 2008. A high n performance liquid chromatography with electrochemical detection for the determination of olanzapine in human plasma. *Acta poloniae pharmaceutical n drug research*, 65 (6) 759-762
38. Boulton, D., W., Markowitz, J., S., & DeVane, C., L. (2001). A high-performance liquid chromatography assay with ultraviolet detection for olanzapine in human plasma and urine. *Journal of Chromatography B: Biomedical Sciences and Applications*, 759(2), 319-323.
39. Chiu, J., A., & Franklin, R., B. (1996). Analysis and pharmacokinetics of olanzapine (LY170053) and two metabolites in rat plasma using reversed-phase HPLC with electrochemical detection. *Journal of pharmaceutical and biomedical analysis*, 14(5), 609-615.
40. D'Arrigo, C., Migliardi, G., Santoro, V., & Spina, E. (2006). Determination of olanzapine in human plasma by reversed-phase high-performance liquid chromatography with ultraviolet detection. *Therapeutic drug monitoring*, 28(3), 388-393.
41. Dusci, L., J., Hackett, L., P., Fellows, L., M., & Ilett, K., F. (2002). Determination of olanzapine in plasma by high-performance liquid chromatography using ultraviolet absorbance detection. *Journal of Chromatography B*, 773 (2), 191-197.
42. Raggi, M., A., Mandrioli, R., Sabbioni, C., Ghedini, N., Fanali, S., & Volterra, V. (2001). Determination of olanzapine and desmethylolanzapine in the plasma of schizophrenic patients by means of an improved HPLC method with amperometric detection. *Chromatographia*, 54(3-4), 203-207.
43. Raggi, M., A., Casamenti, G., Mandrioli, R., Fanali, S., De Ronchi, D., & Volterra, V. (2000). Determination of the novel antipsychotic drug olanzapine in human plasma using HPLC with amperometric detection. *Chromatographia*, 51(9-10), 562-566.
44. Atila karaca, S., & yeniceli uğur, D. (2018). Development of a validated HPLC method for simultaneous determination of olanzapine and aripiprazole in human plasma. *Marmara Pharmaceutical Journal*, 22 (4), 493-501.
45. Pradhan, K., K., Kumari, S., & Samanta, R., (2014). Development and validation of a stability indicating UV spectroscopic method for olanzapine in bulk and pharmaceutical dosage forms, *International Journal Pharmaceutical Sciences*, 6 (4), 67-72.
46. Basavaiah, K., Abdulrahman, S., A., & Vinay, K., B. (2010). New extractive spectrophotometric methods for the determination of olanzapine in pharmaceutical formulations using bromocresol green. *Jordan Journal of Chemistry*, 146 (596), 1-17.
47. Joseph, E., Balwani, G., Nagpal, V., Reddi, S., & Saha, R. (2015). Validated UV Spectrophotometric Methods for the Estimation of Olanzapine in Bulk, Pharmaceutical Formulations and Preformulation Studies. *Brazilian Journal Pharmaceutical Research*, 6, 181-190.
48. Rajendraprasad, N., & Basavaiah, K. (2009). Determination of olanzapine by spectrophotometry using permanganate. *Brazilian Journal of Pharmaceutical Sciences*, 45 (3), 539-550.
49. Salama, F.M., Attia, K.A., Said, R.A., El-Olemy, A., & Abdel-raoof, A., M. (2017). Spectrophotometric Determination of Olanzapine in the Presence of its Acidic Degradation Product; Application of Kinetic Study. *Analytical Chemistry Letters*, 7(5), 663-675.
50. Firdous, S., Aman, T., & Nisa, A. (2005). Determination of olanzapine by UV spectrophotometry and non-aqueous titration. *Journal-Chemical Society of Pakistan*, 27(2), 163.
51. Patel, V.M., Patel, J.A., Havele, S., S., & Dhaneshwar, S., R. (2010). First and second derivative spectrophotometric methods for determination of olanzapine in pharmaceutical formulation. *International Journal Chemical Technical Research*, 2(1), 756-761
52. Revanasiddappa, H., D., & Deepakumari, H., N. (2014). Highly sensitive spectrophotometric method for the quantitative determination of olanzapine in its pure and in pharmaceutical dosage forms. Journal of scientific and industrial research74, 41-45.

53. Fadhel, S., R., Abdulla, N., I., & Sulaiman, I., D. (2017). The Spectrophotometric Determination of Olanzapine via Coupling with Diazotized p-Nitroaniline. *Iraqi Journal of Pharmaceutical Sciences (P-ISSN: 1683-3597, E-ISSN: 2521-3512)*, 25(1), 42-49.
54. Moura, J., & Moita, G., C. (2012). Determinação simultânea de olanzapine e cloridrato de Fluoxetine em formulações farmacêuticas por espectrofotometria derivativa. *Quim. Nova*, 35(3), 627-633.
55. Silva G., M., Köppl, A., Unholzer, S., & Haen, E. (2017). Development and validation of an HPLC-UV method for the simultaneous determination of the antipsychotics Clozapine, olanzapine and quetiapine, several beta-blockers and their metabolites. *Biomedical Chromatography*, 31(10), 39-68.
56. Kumar, S., R., Gayathri, P., Duganath, N., Kiran, C., H., Sridhar, C., & Jayaveera, K., N. (2011). Simultaneous estimation of Fluoxetine HCl and olanzapine in bulk drug and pharmaceutical formulation by using UV-visible spectroscopy method. *International Journal Pharmaceutical Sciences Drug Research*, 3, 52-55.
57. Ghanchivhora, F., I., Shah, J., S., & Maheswari D., M3. (2017). Development and validation of spectroscopic method for simultaneous estimation of paliperidone and olanzapine in syenthetic mixture. *International Journal of Recent Scientific Research*, 8 (4) 16559-16562.
58. Deepakumari, H., N., & Revanasiddappa, H., D. (2012). Sensitive spectrophotometric method for the determination of olanzapine and orphenadrine in pure and dosage forms by ternary complex formation with eosin and lead (II). Chemical Sciences Journal.70, 1-8.
59. Ali, A., A., A., & Elbashir, A., A. (2012). Optimized and Validated Spectrophotometric Method for the Determination of Olanzapine in Pharmaceutical Formulations Using 1, 2,-Naphthoquinone-4-Sulphonate (Nqs). *American Academic & Scholarly Research Journal*, 4(3), 1-15.
60. Adegoke, O., A., Thomas, O., E., Makanjuola, D., M., & Adewole, O., O. (2014). Spectrophotometric determination of olanzapine after condensation with p-dimethylaminobenzaldehyde. *Journal of Taibah University for Science*, 8(3), 248-257.
61. Nagaraju, R., Basavaiah, K., Tharpa, K., & Vinay, K., B. (2009). Quantitative determination of olanzapine in tablets with visible spectrophotometry using cerium (IV) sulphate and based on redox and complexation reactions. *Eurasian Journal of Analytical*, 4(2, Cop), 191-203.
62. Krebs, A., Starczewska, B., Puzanowska-Tarasiewicz, H., & Sledz, J. (2006). Spectrophotometric determination of olanzapine by its oxidation with N-Bromosuccinimide and cerium (IV) sulphate. *Analytical sciences*, 22(6), 829-833.
63. Shah, S., R., B., Shah, N.,J., Patel, D., R., & Patel, N.M.(2008).stability-indicating simultaneous hptlc method olanzapine and Fluoxetine in combined tablet dosage form.*indian journal of pharmaceutical sciences*, 70 (2) 251-255
64. Patel, S., Patel, N., Patel, P., Patel, D., Prajapati, A., & Patel, S. (2009). Validation of a stability-indicating HPTLC method for analysis of duloxetine hydrochloride in capsule dosage form. Separation and analysis of duloxetine hydrochloride and olanzapine in a synthetic mixture. *JPC-Journal of Planar Chromatography-Modern TLC*, 22(2), 121-126.
65. Patel, S. & Patel, N., J. (2009). Simultaneous RP-HPLC and HPTLC estimation of Fluoxetine hydrochloride and olanzapine in tablet dosage forms. *Indian journal of pharmaceutical sciences*, 71(4), 477-480.
66. Patel, R., B., Patel, M., R., Bhatt, K., K., & Patel, B., G. (2010). Development and validation of an HPTLC method for determination of olanzapine in formulations. *Journal association of official analytical chemists International*, 93(3), 811-819.
67. Patel, D.S., Sharma, N., Patel, M., C., Patel, B.N., Shrivastav, P., S., & Sanyal, M. (2012). LC–MS/MS assay for olanzapine in human plasma and its application to a bioequivalence study. *Acta Pharmaceutica Sinica B*, 2(5), 481-494.
68. Zhang, G., Alvin, V., T., Jr, & Michael G., B. (2007) "Liquid chromatography/tandem mass spectrometry method for the simultaneous determination of olanzapine, risperidone, 9-hydroxyrisperidone, Clozapine, haloperidol and ziprasidone in rat plasma." Rapid Communications in Mass Spectrometry. *An International Journal Devoted to the Rapid Dissemination of Up-to-the-Minute Research in Mass Spectrometry*, 21(6) (2007) 920-928.
69. Berna, M., Ackermann, B., Ruterbories, K., & Glass, S. (2002). Determination of olanzapine in human blood by liquid chromatography–tandem mass spectrometry. *Journal of Chromatography B*, 767 (1), 163-168.
70. Bonde, S., L., Bhadane, R., P., Gaikwad, A., Gavali, S., R., Katale, D., U., & Narendiran, A.,

S. (2014). Simultaneous determination of Olanzapine and Fluoxetine in human plasma by LC–MS/MS: Its pharmacokinetic application. *Journal of pharmaceutical and biomedical analysis*, 90, 64-71.

71. Pilla, N., Sreedhar, C., Rao, S., T., & Reddy, V., S. Development and validation of liquid chromatography-tandem mass spectrometry for determination of olanzapine in rabbit plasma. DHR International Journal. Of Pharmaceutical Sciences. (DHR-IJPS). 5 (1) (2014) 88-97.
72. Gopinath, S., Kumar, R.S., Alexander, S. and Danabal, P. (2012). Development of a rapid and sensitive SPE-LC-MS/MS method for the simultaneous estimation of Fluoxetine and olanzapine in human plasma. *Biomedical Chromatography*, 26(9), 1077-1082.
73. Lou, H., G., Ruan, Z., R., Jiang, B., & Chen, J., L. (2015). Simultaneous quantification of olanzapine and its metabolite N-desmethylolanzapine in human plasma by liquid chromatography tandem mass spectrometry for therapeutic drug monitoring. *Biomedical Chromatography*, 29(5), 671-678.
74. Cao, J., Zhang, Z., Tian, Y., Li, Y., & Rui, J. (2012). Liquid Chromatography-Mass Spectrometry Method for the Determination of Olanzapine in Human Plasma and Application to a Bioequivalence Study. *Current Pharmaceutical Analysis*, 8(3), 247-254.
75. Nielsen, M., K., K., & Johansen, S., S. (2009). Determination of olanzapine in whole blood using simple protein precipitation and liquid chromatography-tandem mass spectrometry. *Journal of analytical toxicology*, 33(4), 212-217.
76. Tonooka, K., Yoshida, L., Tomobe, K., Kunisue, Y., Terada, M., & Shinozuka, T. (2018). Sensitive Liquid Chromatography/Tandem Mass Spectrometry Method for the Simultaneous Determination of Risperidone, Olanzapine, Quetiapine, Clozapine, Ziprasidone, Perospirone, Aripiprazole and Blonanserin in Human Serum. *American Journal of Analytical Chemistry*, 9 (2), 88-97.
77. Josefsson, M., Roman, M., Skogh, E., & Dahl, M., L. (2010). Liquid chromatography/tandem mass spectrometry method for determination of olanzapine and N-desmethylolanzapine in human serum and cerebrospinal fluid. *Journal of pharmaceutical and biomedical analysis*, 53(3), 576-582.
78. Chin, C., Zhang, Z., P., & Karnes, H., T., (2004). A study of matrix effects on an LC/MS/MS assay for olanzapine and desmethyl olanzapine. *Journal of pharmaceutical and biomedical analysis*, 35(5), 1149-1167.
79. Urdigere, A., K., R., Besagarahally, B., L., & Basavaiah, K. (2012). Sensitive liquid chromatography–tandem mass spectrometry method for the determination of olanzapine in human urine. *Arabian Journal for Science and Engineering*, 37(5), 1381-1387.
80. Cavalcanti Bedor, N., C., T., Galindo Bedor, D., C., Miranda de Sousa, C., E., Nunes Bonifácio, F., da Mota Castelo Branco, D., Bastos Leal, L. & Pereira de Santana, D. (2015). The development and validation of a method for quantifying olanzapine in human plasma by liquid chromatography tandem mass spectrometry and its application in a pharmacokinetic study. *Clinical and Experimental Pharmacology and Physiology*, 42(3), 305-313.
81. Ni, X., J., Wang, Z.Z., Shang, D., W., Lu, H., Y., Zhang, M., & Wen, Y., G., (2018). Simultaneous analysis of olanzapine, Fluoxetine, and norfluoxetine in human plasma using. *Journal of chromatography* B, 1-37.
82. Nirogi, R., V., Kandikere, V., N., Shukla, M., Mudigonda, K., Maurya, S., Boosi, R., & Yerramilli, A. (2006). Development and validation of a sensitive liquid chromatography/electrospray tandem mass spectrometry assay for the quantification of olanzapine in human plasma. *Journal of pharmaceutical and biomedical analysis*, 41(3), 935-942.