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Inclusive Review on Analytical and Bioanalytical Method of Ziprasidone

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Vikas R. Patil[1*], Prakash S. Sapkale[2], Yogesh A. Chaudhari[3], Umesh A. Mahajan[2], Salman B. Shaikh[4], Vinay V. Sarode[5]

[1] Assistant Professor, Department of Pharmaceutical Chemistry, TSPM's, Trimurti Institute of Pharmacy, Paldhi (Bk): 425103, Jalgaon, Maharashtra, India [2] Assistant Professor, Department of Pharmaceutics, TSPM's, Trimurti Institute of Pharmacy, Paldhi (Bk): 425103, Jalgaon, Maharashtra, India [3] Assistant Professor, Department of Pharmaceutics, Smt. S. S. Patil College of Pharmacy, Chopda: 425107, Maharashtra, India [4] Assistant Professor, Department of Pharmacognosy, TSPM's, Trimurti Institute of Pharmacy, Paldhi (Bk): 425103, Jalgaon, Maharashtra, India [5] Research Scholar, TSPM's, Trimurti Institute of Pharmacy, Paldhi (Bk): 425103, Jalgaon, Maharashtra, India

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ABSTRACT

Ziprasidone (ZRS) is an atypical antipsychotic medication. It is a potent highly selective antagonistic activity on the D_2 and $5HT_2$ receptors. It is used for the treatment of schizophrenia, acute mania and mixed state episodes associated with bipolar disorder. Ziprasidone was approved for medical use in the United State in 2001. Therefore, the main objective of this analysis of ZRS in pharmaceutical and biological formulation is in both qualitative and quantitative terms. In this review article, we have summarized UV/Vis spectroscopy, high-performance liquid chromatography (HPLC), High-performance thin-layer chromatography (HPTLC), Ultra Performance liquid chromatography (UPLC) etc. based methods for estimation of ziprasidone. In addition to that, we have discussed the bioanalytical methods for ZRS analysis. In conclusion, this review article will help to research scholars for further method development for drug estimation in pharmaceutical dosage forms and biological fluids.

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INTRODUCTION

Ziprasidone (ZRS) is atypical antipsychotic drug which belongs to second generation. It is having the G protein-coupled receptor (GPCR) binding property. It has high affinity for serotonergic and dopaminergic receptor. Ziprasidone (ZRS) antagonizes the 5-HT_{2A}, 5-HT_{2C} and D_2 as well as at adrenergic α_1/ α_2 and histamine H_1 receptors [1]. It is used in the treatment of variety of mood and mental health disorders, such as schizophrenia and bipolar disorder [2]. The ziprasidone mesylate was the first novel short-acting intramuscular formulation in the parenteral form for the treatment of acute agitation in patients with schizophrenia. Ziprasidone is characterized by a safe profile with a low risk of extrapyramidal side-effects (EPS), and for the treatment of children and adolescents it is effective and safe [3]. Ziprasidone is a benzisothyazolyl piperazine derivate with antipsychotic property [1]. Ziprasidone (ZRS) chemically known as (5-[2-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl] ethyl]-6-chloro-1,3-dihydroindol-2-one) [2]. **Figure 1** depicts the chemical structure of ZRS.

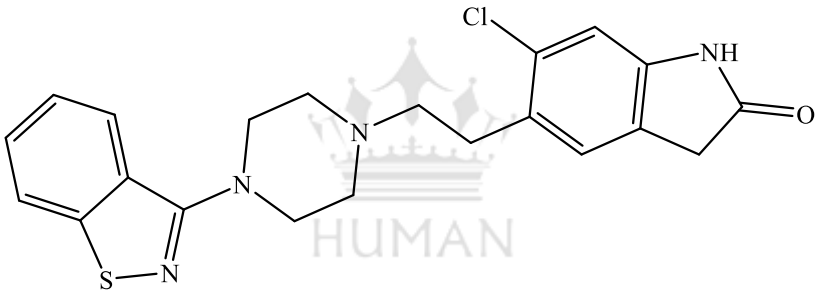

Figure No. 1: Chemical structure of ZRS

MECHANISM OF ACTION

Ziprasidone has extensively 5-HT2A/D2 affinity which binds to multiple 5HT receptors and prevents 5HT and NE reuptake by blocking monoamine transporter. It having low affinity for muscarinic cholinergic M1, histamine H1, and alpha1-adrenergic receptors [4].

PHARMACOKINETICS

Absorption

While administered orally, in absence of food the oral bioavailability of Ziprasidone is 60%, and while taking with meal containing at least 500kcal, its absorption may reaches to 100% [5].

Distribution

The volume of distribution of Ziprasidone is approximately 1 to 1.5 L/kg. It is having high protein binding property (greater than 99%), ziprasidone primarily binding to albumin and α1-acid glycoprotein [5].

Metabolism

Ziprasidone is extensively metabolised in Liver. Metabolism takes place by phase I (primarily cytochrome P450 3A4). The aldehyde oxidase catalyzes the primary reductive pathway, and CYP3A4 catalyzes the other less prominent oxidative pathways [6].

Elimination

Ziprasidone is highly metabolized after oral administration with only a small amount excreted as unchanged form through urine (<1%) or feces (<4%) [6].

PHARMACODYNAMICS

Ziprasidone's main effect is to reduce dopaminergic and serotonergic pathway activity in the brain, which helps to alleviate symptoms of schizophrenia and mood disorders.

ANALYTICAL ACCOUNT OF ZRS

For the determination of ZRS in bulk and pharmaceutical formulations, an exhaustive literature search found numerous analytical techniques such as UV/Visible Spectrophotometry, HPLC, HPTLC, UPLC and bioanalytical approaches. ZRS is measured as a single constituent and in combination with Olanzapine, Risperidone, 9-hydroxyrisperidone, Clozapine, Haloperidol, Chlorpromazine and Buclizine hydrochloride in various dosage forms and Ziprasidone. **Figure 2** shows different analytical methods implemented for the estimation of ZRS.

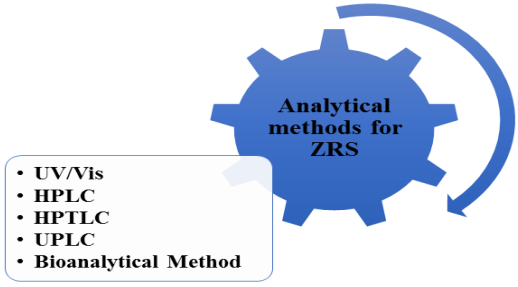

Figure No. 2: Analytical methods of ZRS

Bio-analytical method for ZRS

Bio-analysis is a sub-discipline of analytical chemistry covering the quantitative measurement of xenobiotics (drugs and their metabolites, and biological molecules in unnatural locations or concentrations) and biotics (macromolecules, proteins, DNA, large molecule drugs, metabolites) in biological systems [7]. The summary of the reported bioanalytical methods is shown in **Table 1.**

Table No. 1: Bioanalytical determination of ZRS

Sr. No.	Drug	Sample Matrix	Method	Column	Detection	Internal Standard	Ref.
1	ZRS	Rat Plasma	HPLC	Grace Vydac C18 monomeric column	210 nm	Escitalopram	8
2	ZRS	Human Plasma	HPLC	RP C18 column	320 nm	Mirtazapine	9
3	ZRS	Plasma	LC	Reversed-phase trimethylsilyl bonded silica column	320 and 410 nm	α-ergocryptine	10
4	ZRS	Rat urine	RP-HPLC/UV	Reversed phase column LUNA® C18	210 nm	Vardenafil	11
5	ZRS	Serum or plasma sample	HPLC	ODS Hypersil C18 material	254 nm	Fluperlapine	12
6	ZRS	Human Plasma	LC-MS/MS	C8 column	***	*N*-methyl ziprasidone	13
6	OLZ, RIS, 9-OH RIS, CLOZ, HAL, ZRS	Rat brain tissue	LC-MS/MS	Waters Atlantis™ dC-18 column	***	Midazolam	14
7	OLZ, RIS, 9-OH RIS, HAL, CPZ and ZRS	Rat plasma	HPLC	Agilent Eclipse XDB C8 column	255 nm, 277 nm and 245 nm	Imipramine	15

*** Not Provided

UV-Visible spectroscopy method for ZRS

The spectrophotometric methods have been accounted for the determination of ZRS. This review compiles two single paper describing spectrophotometric methods for determination of alone ZRS and one paper describing spectrophotometric methods for determination of ZRS and BUCZ. The details of Spectrophotometry determination of basic principle, sample

matrix, lambda max, solvent linearity range and the correlation coefficient are summarized in **Table 2.**

Table No. 2: Spectrophotometric methods used for determination of ZRS

Sr. No.	Drug	Matrix	Solvent	Lambda Max (nm)	Linearity (µg/mL)	Correlation coefficient (R2)	Ref.
1	ZRS	Bulk and Formulation	Saline buffer pH 7.4	318 nm	2-10 µg/ml	0.9998	16
2	ZRS	Bulk and Dosage form	0.1 N hydrochloric acid	490 nm	2-10 µg/ml	0.99940	17
3	ZRS and BUCZ	Bulk and Pharmaceutical formulation	Isopropyl alcohol and Chloroform	420 nm	2.5-15.0 µg/ml	0.9997 and 0.9999	18

High-performance liquid chromatography (HPLC) methods for ZRS

The specificity of the HPLC method is excellent and simultaneously sufficient precision is also attainable. However, it has to be stated that the astonishing specificity, precision, and accuracy are attainable only if wide-ranging system suitability tests are carried before the HPLC analysis. For this reason, the expense to be paid for the high specificity, precision, and accuracy is also high [19]. The summary of the reported HPLC methods is shown in **Table 3.**

Table No. 3: Summary of HPLC methods for the determination of ZRS

Sr. No.	Drug name	Column	Mobile phase	Lambda max(nm)	Linearity (µg/mL)	Retention time (min)	Flow rate (mL/min)	Detector	Ref.
1	ZRS	ODS C18 column	Methanol and phosphate buffer (55:45v/v)	314 nm	0.5-30 µg/mL	4.522 min	1 mL/min	UV	20
2	ZRS	Agilent zorbax C-8 column	Methanol and potassium dihydrogen orthophosphate buffer at pH 3.0	229 nm	25% to 150 %	22.2 min	1.5 ml/min	PDA	21
3	ZRS	Welchrom C18 isocratic column	Acetonitrile: Water (50:50 v/v), adjusted to pH 3.3 with OPA	251 nm	2-10 µg/mL	6.707 min	1.0 mL/min	UV	22
4	ZRS	Lichrospher RP-18 column	20 mM ammonium acetate (pH adjusted to 3.0 with OPA) and methanol(30:70 %v/v)	225 nm	1-500 µg/mL	4.76 min	1 mL/min	UV	23
5	ZRS	Waters Spherisorb® octadecylsilyl 1 column	**Mobile phase A** [buffer–acetonitrile (80 + 20, v/v)] **Mobile phase B** [buffer–acetonitrile (10 + 90, v/v)]	250 nm	70-130 µg/mL	7.9 min	1.5 mL/min	DAD	24
6	ZRS	ACE-5 C18 column	Acetonitrile : Phosphate Buffer pH 3.2 in the ratio of (40:60)	219 nm	10-50 µg/ml	2.83 min	1ml/min	UV	25
7	ZRS	Lichrosorb RP C18 column	Water: acetonitrile: phosphoric acid (76:24:0.5 v/v/v)	229 nm	10–500 µg/ml	19.14 min	1.5 ml/min	DAD	26
8	ZRS	Zorbax SB C-8 column	Buffer (pH= 3.0) and methanol (45:55 v/v)	229 nm	58.21 µg/ml and 396.63 µg/ml	1.2 min	0.9 ml/min	PDA	27
9	ZRS	XBridge C8 column	Buffer:methanol (60:40)	229 nm	***	3.88 min	1.5 mL/min	UV	28

*** Not Provided

High-performance thin layer chromatography (HPTLC) method for ZRS

Thin-layer chromatography is a popular technique for the analysis of a wide variety of organic and inorganic materials, because of its distinctive advantages such as minimal sample clean-up, a wide choice of mobile phases, flexibility in sample distinction, high sample loading capacity and low cost. ***Robert Skibiński and Lukasz Komsta*** established Validation of NP-HPTLC and RP-HPTLC methods with video densitometric detection for analysis of ziprasidone in pharmaceutical formulations. TLC was carried out by stationary phase of NP-HPTLC and RP-HPTLC are silica gel 60 F_{254} plates and RP8 F_{254} plates with hexane-dioxane-propyl amine 1:9:0.4 (v/v) and tetrahydrofuran-pH 9.0 phosphate buffer 5:5 (v/v) as mobile phase. The linearity range of ZRS of NP-HPTLC and RP-HPTLC are 0.2–1.2 µgper spot and 0.1-1.1 µgper spot respectively. The developed method was successfully applied for determination of ziprasidone in formulation [29].

Ultra-Performance liquid chromatography (UPLC) method for ZRS

The introduction of UPLC offers faster analytical separation procedures without sacrificing the high-quality results [30]. Many laboratory specialists assured that the UPLC can eventually replace all current HPLC methods. In addition, it is an advanced technology that combines the unique characteristics and outperforms HPLC in several aspects, including greater chromatographic resolution, more sensitive analysis, less time consumption; [31-35] reduced solvent use, and fast analytical speed [36-38].

Table No. 4: Summary of UPLC methods for the determination of ZRS

Sr. No.	Drug	Stationary phase	Mobile phase	Flow rate (mL/min)	Detection wavelength (nm)	Ref.
1	ZRS	Acquity UPLC BEH C18 (50 mm x 2.1 mm x 1.7 µm) column	10 mM ammonium-formate buffer and acetonitrile	0.3 ml/min	***	39
2	ZRS	Zorbax Eclipse-C18 (2.1 x 50mm, dp =1.8 mm) column	Methanol and water with addition of 0.1% solution of formic acid	0.4ml/min	254 nm	40
3	ZRS	Acquity UPLC BEH 100-mm, 2.1-mm, and 1.7-lm Shield RP-18 columns	0.25% orthophosphoric acid (pH of 2.0)	0.3ml/min	230nm	41
4	ZRS	ACQUITY UPLC BEH C8, 2.1 x 50 mm, 1.7 µm (USP designation: L7), part number 186002877	Buffer:methanol (60:40)	0.6 mL/min	229 nm	42

*** Not provided

CONCLUSION

The present review article provides comprehensive data of various analytical and bioanalytical methods developed for ZRS alone and in combinations. For analysis purpose, different analytical methods have been reported that includes HPLC, HPTLC, UPLC, UV spectroscopy, etc. The method along with their details concerning the mobile phase, stationary phase, retention time, etc., have been summarized in tabular form that will more helpful for the researchers for further analytical method development for estimation of ZRS in dosage form and pure form. In the future, enlisted data can be used for the development of analytical methods bio-analysis of ZRS in pharmaceutical and biological formulations. Finally, it presents an opportunity for greater information on what has already been done and what new methods and changes can be developed to get a better estimation of ZRS.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATION

1) **ZRS**- Ziprasidone
2) **UV/VIS** - Ultra violet/visible spectroscopy
3) **HPLC** - High-performance liquid chromatography
4) **HPTLC** - High-performance thin layer chromatography
5) **LC-MS/MS** - Liquid chromatography-mass spectroscopy-mass spectroscopy
6) **UPLC** -Ultra performance liquid chromatograph
7) **GPCR**- G-protein coupled receptor
8) **EPS**- Extrapyramidal side-effects
9) **L/kg** - Kilogram per liter
10) **DNA**- Deoxyribose nucleic acid
11) **LC**- Liquid chromatography

12) **OLZ**- Olanzapine

13) **9-OH** - 9-hydroxyrisperidone

14) **RIS**- Risperidone

15) **CLOZ**- Clozapine

16) **HAL**- Haloperidol

17) **CPZ**- Chlorpromazine

18) **BUCZ**- Buclizine hydrochloride

19) **µg/mL** - Micro gram per Milliliter

20) **pH**- Potential of hydrogen

21) **DAD** - Diode array detector

22) **mL/min**- Milliliters per minute

23) **nm** - Nanometer

24) **TLC** - Thin layer chromatography

25) **DAD** - Diode array detector

26) **PDA** - Photo diode array

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