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Method Development and Validation for Estimation of Ziprasidone in marketed formulation by using RP-HPLC

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Abstract:

Proposed method was found to be linear in the range of 5-25 µg/ml Ziprasidone with the correlation coefficient near to one respectively. The validation and the reliability of proposed method were assessed by recovery study. The recovery of added standards (80%, 100% 120%) was ranging from 99.62 to 99.784%, for Ziprasidone. Liquid chromatographic system from waters comprising of manual injector, Waters 515 binary pump for constant flow and constant pressure delivery and U.V. detector connected to data ace software controlling the instrumentation as well as processing methanol: Acetonitrile in the ratio of 50:50 v/v at a flow rate of 1.0 ml min^{-1}. A thermo C-18 column (4.6 x 250mm, 5µ particle size) was used as the stationary phase, 250.0 nm was selected as the detection wavelength for UV-vis. detector. The proposed methods were found to be linear in the range of 5-25 µg/ml with correlation coefficient close to one. Precision was determined by repeatability, Intermediate precision and reproducibility of the drugs. The robustness of developed method was checked by changing in the deliberate variation in solvent. The result obtained shows the developed methods to be Cost effective, Rapid (Short retention time), Simple, Accurate (the value of SD and
%RSD less than 2), Precise and can be successfully employed in the routine analysis of these drugs in bulk drug as well as in tablet dosage form.

Key word: Ziprasidone, Method development, Validation, HPLC, Dosage form.

INTRODUCTION: Chromatography is a separation process that is achieved by distributing the components of a mixture between two phases, a stationary phase and a mobile phase. Those components held preferentially in the stationary phase are retained longer in the system than those that are distributed selectively in the mobile phase. As a consequence, solutes are eluted from the system as local concentrations in the mobile phase in the order of their increasing distribution coefficients with respect to the stationary phase; a separation is achieved. Due to several advances made in the chromatographic techniques, it can be used for separation, identification and quantification purposes. Modern pharmaceutical formulations are complex mixtures containing one or more therapeutically active ingredients, to a number of inert materials like diluents, disintegrants, colors and flavors. In order to ensure quality and stability of the final product, the pharmaceutical analyst must be able to separate the mixtures into individual components prior to quantitative analysis. Retention of the solutes by the stationary phase may be achieved by one or a combination of mechanisms. Certain substances, such as alumina or silica gel, interact with the solutes primarily

by adsorption, either physical adsorption, in which the binding forces are weak and easily reversible, or chemisorptions, where strong bonding to the surface can occur. Another important mechanism of retention is partition, which occurs when the solute dissolves in the stationary phase, usually a liquid coated as a thin layer on the surface of an inert material or chemically bonded to it. In adsorption chromatography, the mobile phase containing the dissolved solutes passes over the surface of the stationary phase. Retention of the component and their consequent separation depends on the ability of the atoms on the surface to remove the solutes from the mobile phase and adsorb them temporarily by means of electrostatic forces. Usually silica or alumina is utilized as the adsorbent with relatively non-polar solvents such as hexane as the mobile phase in normal phase adsorption whereas in reversed phase adsorption non polymer beds with relative polar solvents such as water, Acetonitrile and Methanol are used as mobile phase. In partition chromatography an inert solid material such as silica gel or diatomaceous earth serves to support a thin layer of liquid which is the effective stationary phase. As the mobile phase containing the solutes passes in close proximity to this liquid phase, retention and separation occurs due to the solubility of the analytes in the two fluids as determined by their partition coefficients. The method suffers from disadvantage due to some solubility of stationary phase in the mobile phase. Hence precautions must be taken to limit dissolution of stationary phase. In ion exchange chromatography the stationary phase consists of a polymeric resin matrix on the surface of ionic functional groups, eg., carboxylic acids or quaternary amines, have been bonded chemically. As the mobile phase passes over this surface, ionic solutes are retained by forming electrostatic chemical bonds with the functional groups. The mobile phase used in this type is always liquid. In size exclusion chromatography the stationary phase is a polymeric substance containing numerous pores of molecular dimensions. Solutes whose molecular size is sufficiently small will leave the mobile phase to diffuse into the pores. Large molecules, which will not fit into the pores, remain in the mobile phase and are not retained. This method is mostly suitable for the separation of mixtures in which the solutes vary considerably in molecular size. The mobile phase in this type may be either liquid or gaseous. The major Chromatographical methods which are employed for analytical purpose. Liquid chromatography is based upon the phenomenon that, under the same conditions, each component in a mixture interacts with its environment differently from other components. Since HPLC is basically a separating technique, it is always used in conjunction with another analytical tool for quantitative and qualitative analysis. Advances in column technology, are high pressure pumping systems and sensitive detectors which have transformed liquid column chromatography into a high speed, high efficiency method of separation. This advanced technology is based upon the use of small bore (2.5 mm – internal diameter) columns and small particle size (3-50 µm) that allow fast equilibrium between stationary and mobile phases. This small particle column technology requires high pressure pumping system capable of delivering the mobile phase at high pressure, as much as 300 atmospheres, to achieve flow rates of several ml per minute. Since it is often necessary to use small amounts of analyte (usually less than 20 µg) with the column packing, sensitive detectors are needed. In normal phase mode, the stationary phase (e.g. silica gel) is polar in nature and the mobile phase is non-polar. In this technique, non-polar compounds travel faster and are eluted first. This is because less affinity between solute and stationary phase. Polar compounds are retained for longer time in the column because more affinity towards stationary phase and takes more time to be eluted from the column. In reverse phase technique, a non-polar stationary phase is used. The mobile phase is polar in nature. Hence polar components get eluted first and non-polar compounds are retained for a longer time. Since most of the drugs and pharmaceuticals are polar in nature, they are not retained for a longer time and eluted faster.

Methodology

In the present work a simple, selective, rapid, precise and economical UV spectrophotometric and reverse phase HPLC method have been developed and validated for the estimation of Ziprasidone in marketed formulation.

Method- RP-HPLC

Table 1: Chemical reagent used

Chemicals/Reagents	Grade	Company
Acetonitrile	HPLC	Merck
Methanol	HPLC	Merck
Potassium dihydrogen phosphate	AR	Rankem
Water	HPLC	Milli-Q
Triethanolamine	AR	Thomas Baker
Orthophosphoric acid	AR	Hi Media

Table 2: Working standard/API

Working standard	Potency
Ziprasidone	99.9%

Table 3: Commercial formulations

Name	Company
Company name	GEODON
Strength	**Ziprasidone** – 20 mg Capsules

Table 4: Instrument specification

HPLC	Waters
Pump	515 Binary pump
Injector	Rheodyne injector with a 20-microlitre loop
Detector	U.V. Vis. detector
Software	Data ace software
Column	Thermo C-18 column (4.6 x 250mm, 5µ particle size)
Balance	Citizen (Cx-265)

Millipore	Mili- Q
Sonicator	PCI (Mumbai)

Identification and Characterization of drugs

Solubility

Solubility of all three drugs was observed by dissolving them in different solvents.

Table 5: Solubility of drug in different solvents

Solvent	**Solubility**
	Ziprasidone
Water	Slightly soluble
0.1N HCl	Slightly soluble
0.1N NaoH	Slightly soluble
Methanol	Soluble
Acetonitrile	Soluble
Ethanol	Soluble
Phosphate Buffer	Slightly soluble

Melting point- M.P. of the drug for Ziprasidone 180-182^{o}C found through Melting point apparatus.

Determination of λ max of Drugs

Standard solution (10µg/ml) of pure, Ziprasidone was prepared. The pure drug solution was scanned on UV spectrophotometer, and λmax determined.

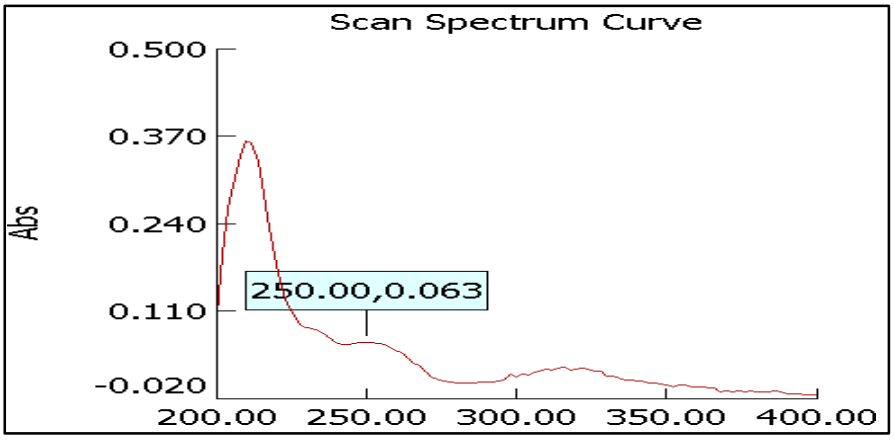

Figure 1: Determination of λmax of Ziprasidone

Selection of Mobile Phase

Initially to estimate Ziprasidone in fix dosage form number of mobile phase in different ratio were tried. A result was shown in Table.

Taking into consideration the system suitability parameter like RT, Tailing factor, No. of theoretical plates and HETP, the mobile phase found to be most suitable for analysis was Methanol: Acetonitrile in the ratio of 50:50 v/v. The mobile phase was filtered through 0.45µ filter paper to remove particulate matter and then degassed by sonication. Flow rate employed for analysis was 1.0 ml/min.

Procedure for preparation of mobile phase

100 ml of methanol and 100ml of acetonitrile Filtered through 0.45 µ filter paper.

Table 6: Mobile phase selection

Mobile Phase	**Ratio**	**Retention Time**
		Remark
Methanol : water	50 : 50 v/v	Poor resolution
Acetonitrile : Metanol	50 : 50 v/v	Most Suitable

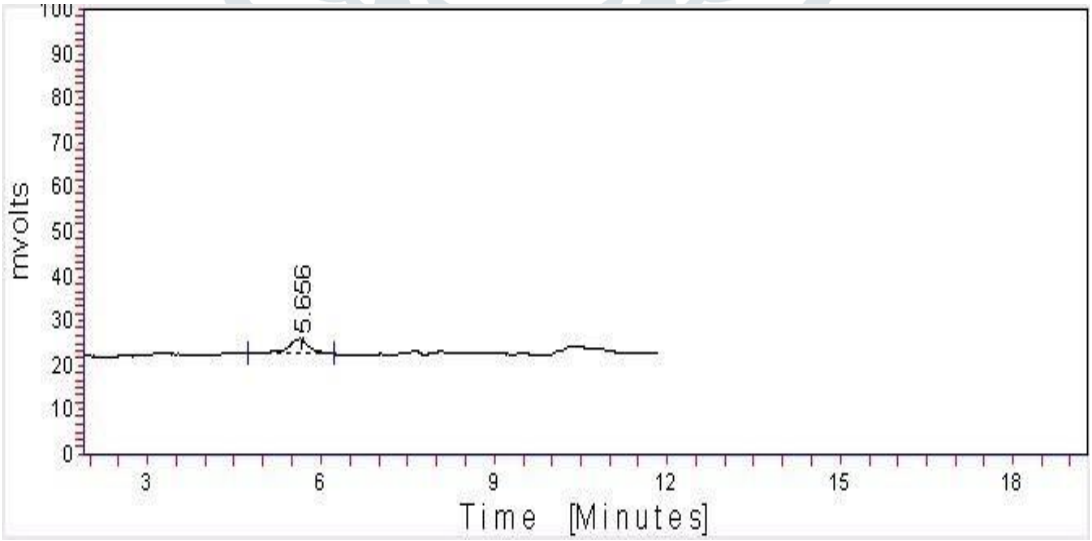

Figure 2: Trail graph of methanol: water

Selection of diluent

Diluent used for preparation of sample were compatible with mobile phase and no any significant affect retention and resolution of analyte. After various trials methanol was used as diluents.

Selection of separation variable

Table 7: Separation variable

Variable	**Condition**
Column	Thermo
Dimension.	250mm x 4.60mm
Particle Size	5µ
Bonded Phase	Octadecylsilane (C_{18})
Mobile Phase	
Methanol	50
Acetonitrile	50
Diluent	Methanol
Flow rate	1.0 ml/min
Temperature	Ambient
Sample Size	20 µl
Detection wavelength	250 mm
Retention time	
Ziprasidone	3.989 ± 0.3 min.

1. Preparation of standard stock solution Accurately weighed 10 mg of Ziprasidone was transferred into 50 ml volumetric flasks and dissolved in 10 ml of Methanol, then volume was made up to 50 ml with acetonitrile and vortex it to get complete dissolution of drug. Stand it aside for few minute, Concentration of Ziprasidone was 200 µg/ml. (stock- A)

2. Preparation of Sub Stock Solution 5 ml of solution was taken from stock-A of Ziprasidone transferred into 10 ml volumetric flask separately and diluted up to 10 ml with diluent (Methanol) to give concentration of 100 µg/ml (Stock-B).

3. Preparation of Different Solution

0.5ml, 1.0 ml, 1.5ml, 2.0ml and 2.5ml of stock-B was taken separately in 10 ml volumetric flask and volume was made up to 10ml with (Methanol). This gives the solutions of 5µg/ml, 10µg/ml, 15µg/ml, 20µg/ml, 25µg/ml for drug.

4. Linearity and Calibration Graph

To establish the linearity of analytical method, a series of dilution ranging from 5-25

µg/ml was prepared. All the solution were filtered through 0.2µm membrane filter and injected, chromatograms were recorded at 254 nm and it was repeat for three times. A calibration graph was plotted between the mean peak area and respective concentration and regression equation was derived.

Table 8: Linearity of Ziprasidone

Standard Concentration µg/ml	**Area under Curve (AUC)**						**Mean**
	Rep-1	**Rep-2**	**Rep-3**	**Rep-4**	**Rep-5**	**Rep-6**	
0	**0**	0	0	0	0	0	0
5	301.972	305.698	308.758	310.458	315.478	320.458	310.470
10	610.564	625.654	625.458	630.478	635.487	640.785	628.071
15	929.502	935.658	930.547	932.478	938.741	940.478	934.567
20	1218.196	1224.589	1220.478	1225.458	1230.478	1235.478	1225.780
25	1536.512	1539.789	1540.785	1550.458	1545.785	1542.458	1542.631
Correl Coeff (r^2)	0.999	0.999	0.999	0.999	0.999	0.999	0.999
Slope (m)	61.43	61.51	61.39	61.71	61.58	61.46	61.51
Intercept (c)	-1.745	2.925	3.563	3.51	7.863	11.58	4.616

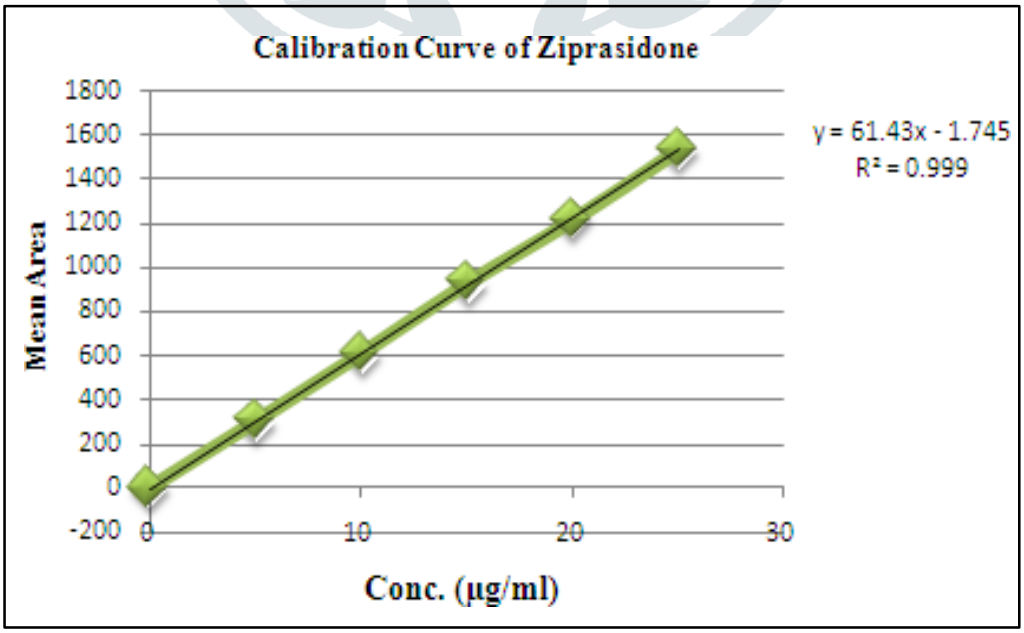

Figure 3: Calibration Curve of Ziprasidone

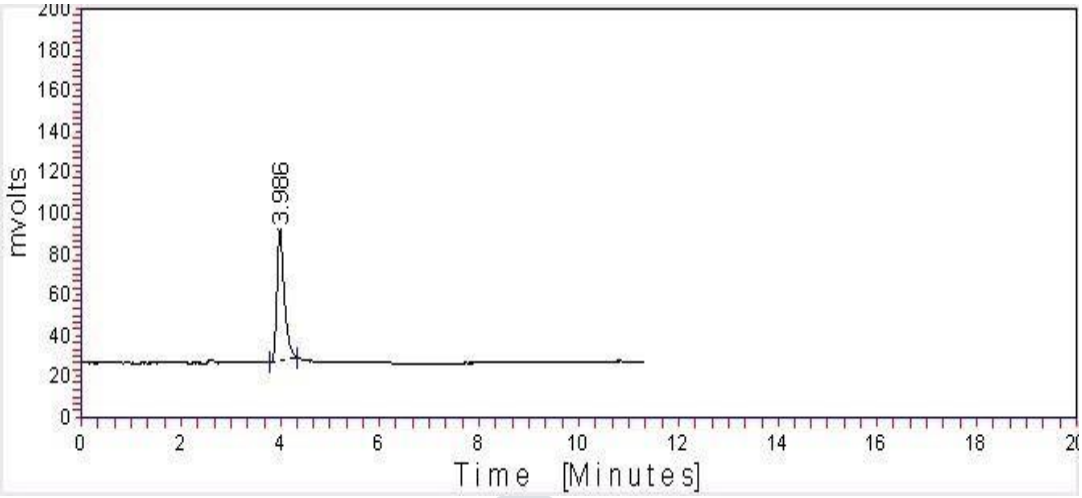

Figure 4: Chromatogram of Ziprasidone

System Suitability Parameters

Separation variables were set and mobile phase was allowed to saturate the column at

1.00 ml/min. After complete saturation of column, three replicates of working standard of Ziprasidone 10 µg/ml was injected separately. Peak report and column performance report were recorded for all chromatogram.

Table 9: System suitability parameters of Ziprasidone

System suitability Parameter →	RT	AUC	No. of theoretical plates	Tailing factor
Rep-1	3.988	610.564	3550	0.98
Rep-2	3.989	625.654	3540	0.95
Rep-3	3.987	625.458	3546	0.96
Rep-4	3.989	630.478	3585	0.93
Rep-5	3.988	635.487	3545	0.96
Rep-6	3.989	640.785	3554	0.95
Mean	3.989	628.071	3553.33	0.955
S.D.	0.001	10.4077	16.219	0.0164
% R.S.D.	0.025	1.65709	0.456	1.7205

Validation of Developed Method

A. Linearity

Linearity of analytical procedure is its ability (within a given range) to obtain test, which are directly proportional to area of analyte in the sample. The calibration plot was contracted after analysis of five different (from 5 to 25 µg/ml) concentrations and areas for each concentration were recorded three times, and mean area was calculated. The regression equation and correlation coefficient of curve are given and the standard calibration curve of the drug is shown in figure. From the mean of AUC observed and respective concentration value, the response ratio (response factor) was found by dividing the AUC with respective concentration.

Table 10: Response ration data for linearity of Ziprasidone

Replicates	**Concentration (µg/ml)**	**Mean AUC**	**Response Ratio**
Rep-1	5	301.972	60.3944
Rep-2	10	610.564	61.0564
Rep-3	15	929.502	61.9668
Rep-4	20	1218.196	60.9098
Rep-5	25	1536.512	61.46048
Mean			61.15758
SD			0.591748
%RSD			0.967579

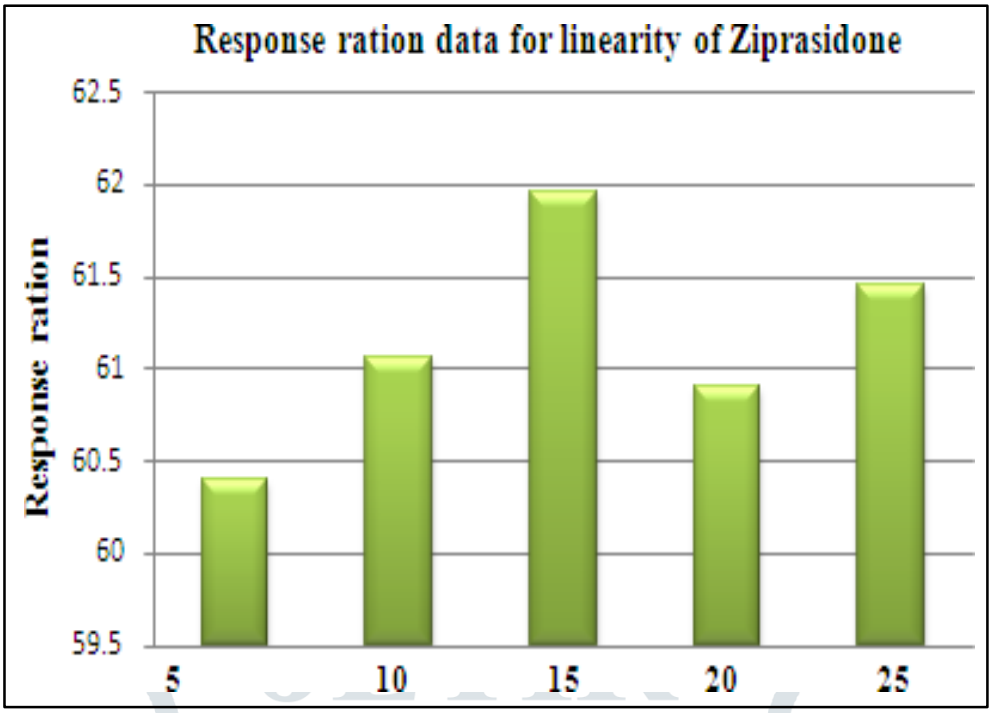

Figure 5: Response Ratio Curve of Ziprasidone

Specificity

Specificity of the method was carried out to assess unequivocally the analyte presence of the components that might be expected to be present, such as impurities, degradation products and matrix components.

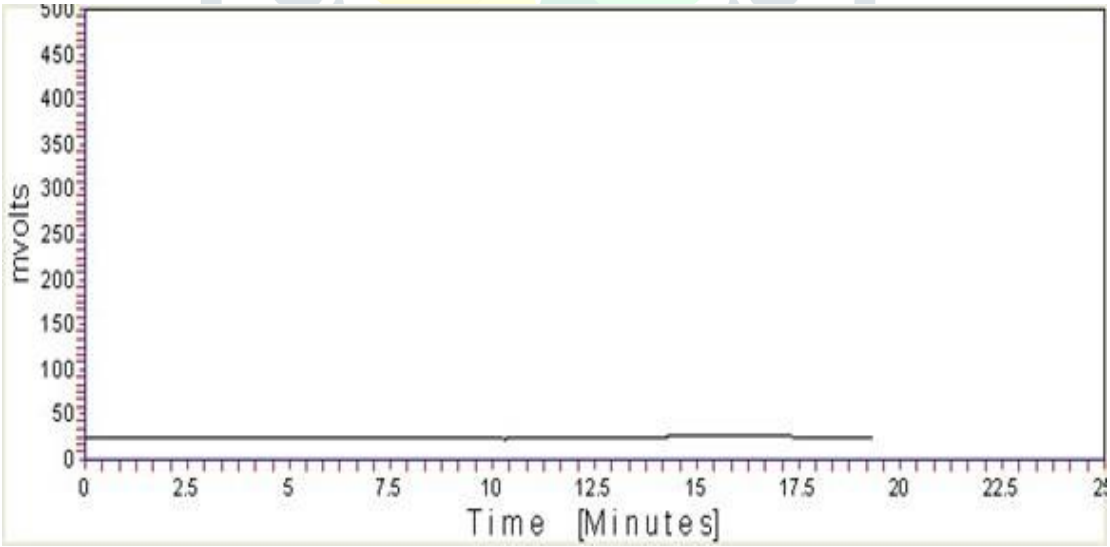

Figure 6: Chromatogram of blank diluent

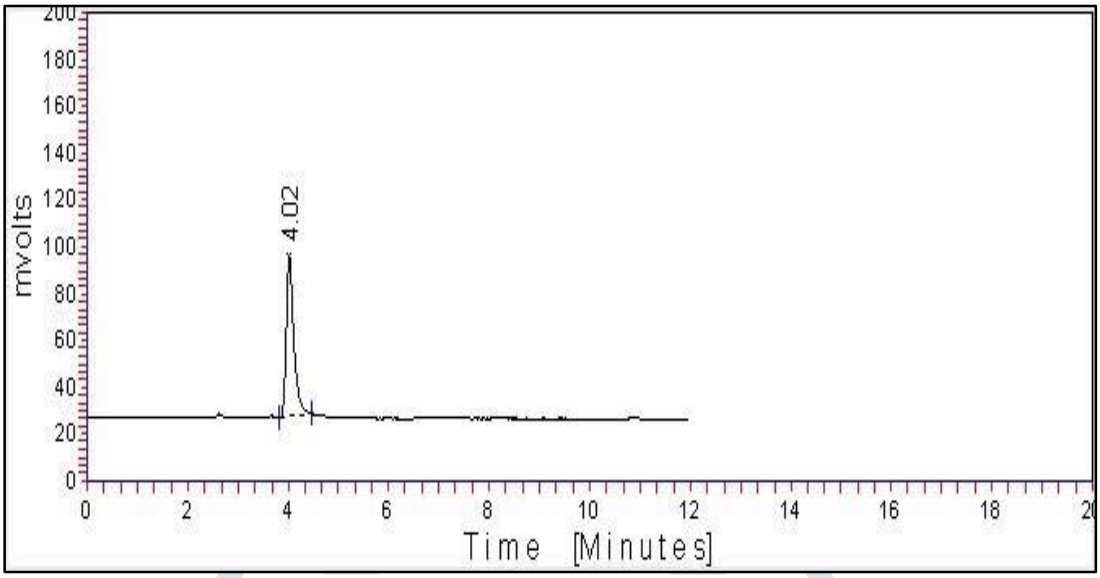

Figure 7: Chromatogram of pure drug

Accuracy

Recovery studies were performed to validate the accuracy of developed method. To preanalysed sample solution, a definite concentration of standard drug (80%, 100%, and 120%) was added and then its recovery was analyzed.

Table 11: Recovery study of Ziprasidone (80% Level)

Conc. of sample (µg/ml)	Amt. Added (µg/ml)	Conc. Found. (µg/ml)			% conc. Found			Mean % conc.
		Rep-1	Rep-2	Rep-3	Rep-1	Rep-2	Rep-3	
5	**4**	3.95	4.01	3.98	98.75	100.25	99.50	99.50
10	**8**	7.99	7.98	7.95	99.88	99.75	99.38	99.67
15	**9.6**	9.59	9.56	9.56	99.90	99.58	99.58	99.69
MEAN **SD** **% RSD**								99.62 0.084 0.084

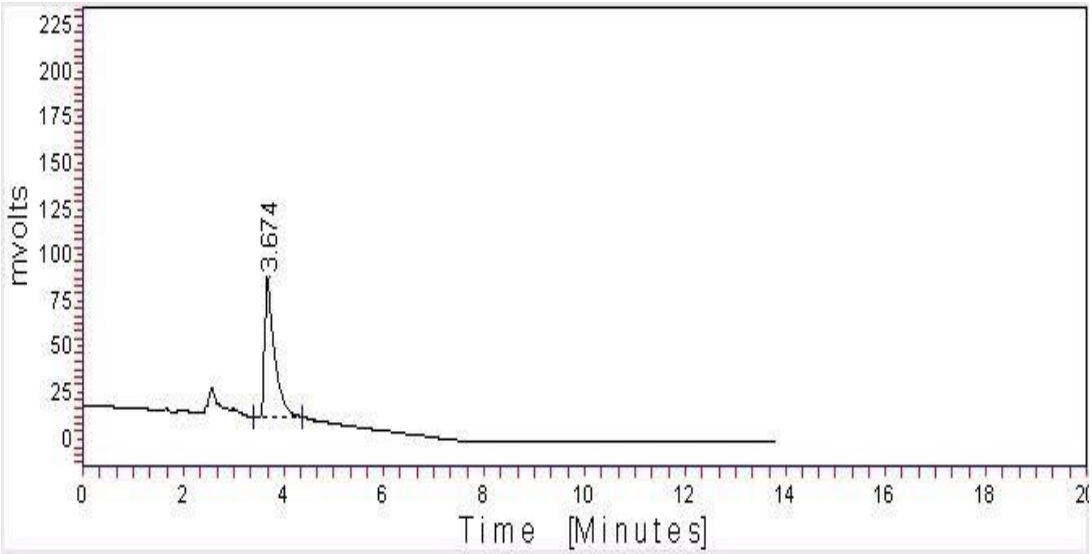

Figure 8: Graph of Recovery study of Ziprasidone (80% Level)

Table 12: Recovery study of Ziprasidone (100% Level)

Conc. of sample (μg/ml)	Amt. Added (μg/ml)	Conc. Found. (μg/ml)			% conc. Found			Mean % conc.
		Rep-1	Rep-2	Rep-3	Rep-1	Rep-2	Rep-3	
5	5	4.98	4.95	5.01	99.60	99.00	100.20	99.60
10	10	9.98	9.99	9.95	99.80	99.90	99.50	99.73
15	15	14.95	14.98	14.99	99.67	99.87	99.93	99.82
MEAN								99.719
SD								0.091
% RSD								0.092

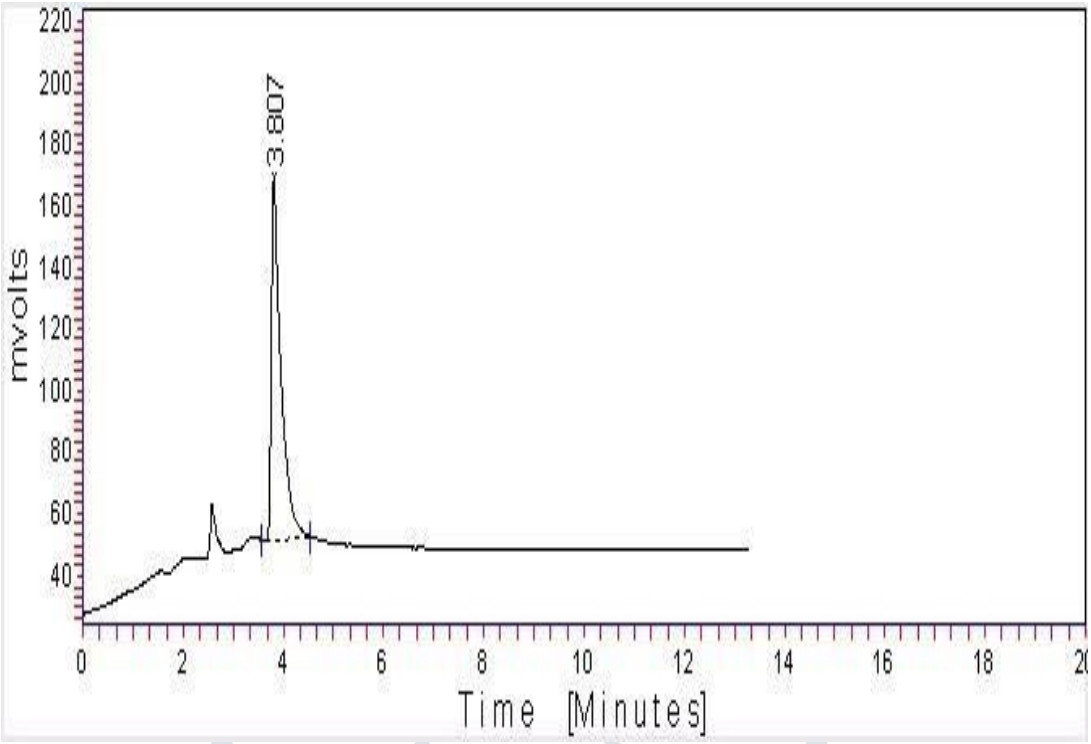

Figure 9: Graph of Recovery study of Ziprasidone (100% Level)

Table 13: Recovery study of Ziprasidone (120% Level)

Conc. of sample (µg/ml)	Amt. Added (µg/ml)	Conc. Found. (µg/ml)			% conc. Found			Mean %conc
		Rep-1	Rep-2	Rep-3	Rep-1	Rep-2	Rep-3	
5	**6**	5.95	5.98	5.99	99.17	99.67	99.83	99.56
10	**12**	11.95	11.98	12.01	99.58	99.83	100.8	99.83
15	**18**	17.98	18.01	17.99	99.89	100.6	99.94	99.96
MEAN								99.784
SD								0.170
% RSD								0.170

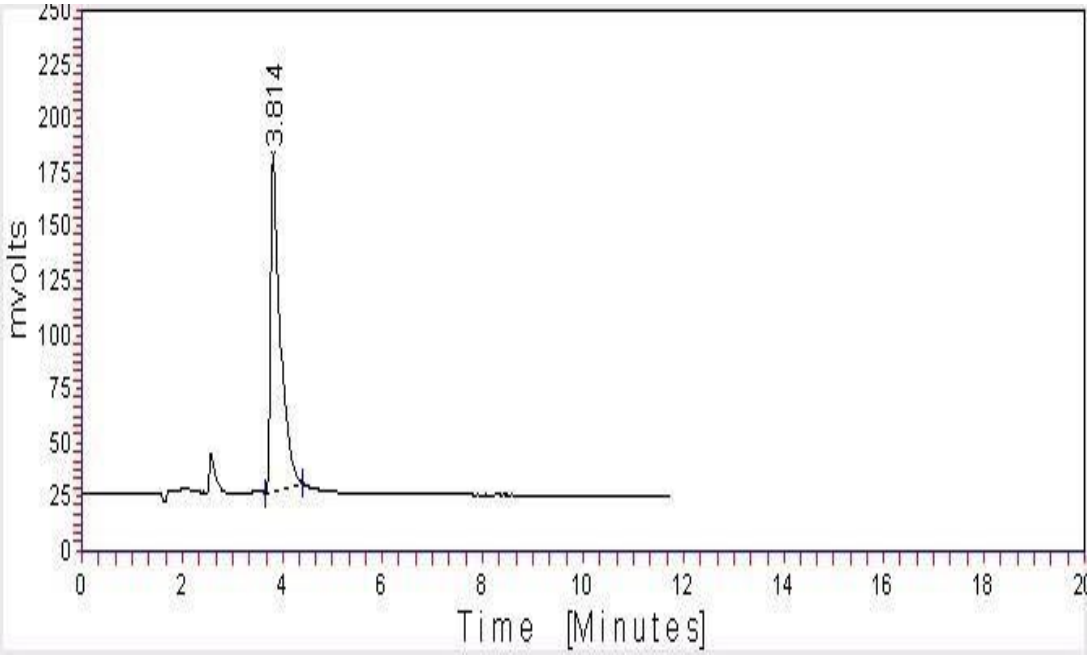

Figure 10: Graph of Recovery study of Ziprasidone (120% Level)

Precision

The stock solution was prepared as stated in 5.4.6. The precision are established in three differences:

1. Repeatability
2. Intermediate precision

a) Day to Day

b) Analyst to Analyst

3. Reproducibility

Repeatability

The repeatability was performed for five replicate at five concentrations in linearity range 5, 10, 15, 20 and 25 µg/ml for Ziprasidone indicates the precision under the same operating condition over short interval time. Results of repeatability are reported in table respectively.

Table 14: Repeatability of Ziprasidone

CONC. REP.	CONCENTRATION FOUND (μg/ml)					MEAN
	5	10	15	20	25	
Replicate-1	4.98	10.01	14.95	19.97	24.91	
Replicate-2	4.97	9.98	14.88	19.96	24.95	
Replicate-3	5.01	10.02	14.98	19.95	24.89	
Replicate-4	4.98	10.01	14.87	19.96	24.96	
Replicate-5	4.99	10.01	14.92	19.89	24.94	
MEAN	4.986	10.006	14.920	19.946	24.930	
% MEAN	99.720	100.060	99.467	99.730	99.720	99.739
SD	0.015	0.015	0.046	0.032	0.029	0.028
% RSD	0.015	0.015	0.047	0.032	0.029	0.028

Intermidiate Precision

a) Day To Day Precision

Intermediate precision was also performed within laboratory variation on different days in five replicate at five concentrations. Results of day to day intermediate precision for Ziprasidone reported in table respectively.

Table 15: Day-to-Day variation of Ziprasidone

CONC. REP.	CONCENTRATION FOUND (μg/ml)					MEAN
	5	10	15	20	25	
Replicate-1	4.93	9.95	14.98	19.97	24.91	
Replicate-2	4.98	9.89	14.95	19.96	24.92	
Replicate-3	4.87	9.85	14.89	19.95	24.97	
Replicate-4	4.89	9.9	14.92	19.87	24.89	
Replicate-5	4.95	9.92	14.96	19.85	24.91	
MEAN	4.924	9.902	14.940	19.920	24.920	
% MEAN	98.480	99.020	99.600	99.600	99.680	99.276
SD	0.044	0.037	0.035	0.056	0.030	0.041
% RSD	0.904	0.374	0.237	0.280	0.120	0.383

Robustness

As per ICH norms, small, but deliberate variations in concentration of the mobile phase were made to check the method's capacity to remain unaffected. The ratio of mobile phase was change from, methanol: acetonitrile (50:50 % v/v), to (45:55 % v/v).Results of robustness are reported in table.

Table 16: Robustness of Ziprasidone

CONC. / REP.	CONCENTRATION FOUND (μg/ml)					MEAN
	5	**10**	**15**	**20**	**25**	
Replicate-1	4.98	9.95	14.95	19.92	24.88	
Replicate-2	4.95	9.95	14.93	19.95	24.95	
Replicate-3	4.95	9.93	14.73	19.98	24.88	
Replicate-4	4.9	9.89	14.89	19.95	24.58	
Replicate-5	4.82	9.96	14.95	19.92	24.95	
MEAN	4.928	9.914	14.91	19.936	24.916	
% MEAN	98.56	99.14	99.4	99.68	99.664	99.458
SD	0.046	0.085	0.08	0.038	0.052	0.065
% RSD	0.934	0.861	0.534	0.19	0.21	0.546

a. Detection Limit and Quantitation Limit

b. The LOD and LOQ of developed method were calculated based on the standard deviation of response and slope of the linearity curve.

Table 17: LOD and LOQ

Name	LOD (μg/ml)	LOQ (μg/ml)
Ziprasidone	0.095	0.271

Analysis of Tablet Sample

Twenty tablets were taken and their average weight was determined. They are crushed to fine powder; amount equal to 10 mg of Ziprasidone was taken in 100-ml volumetric flask. The volume is made up to the mark by mobile phase and filtered by whatmann filter paper (no.41) and the filtrate was used to prepare samples of different concentration. Results of tablet analysis are reported in table.

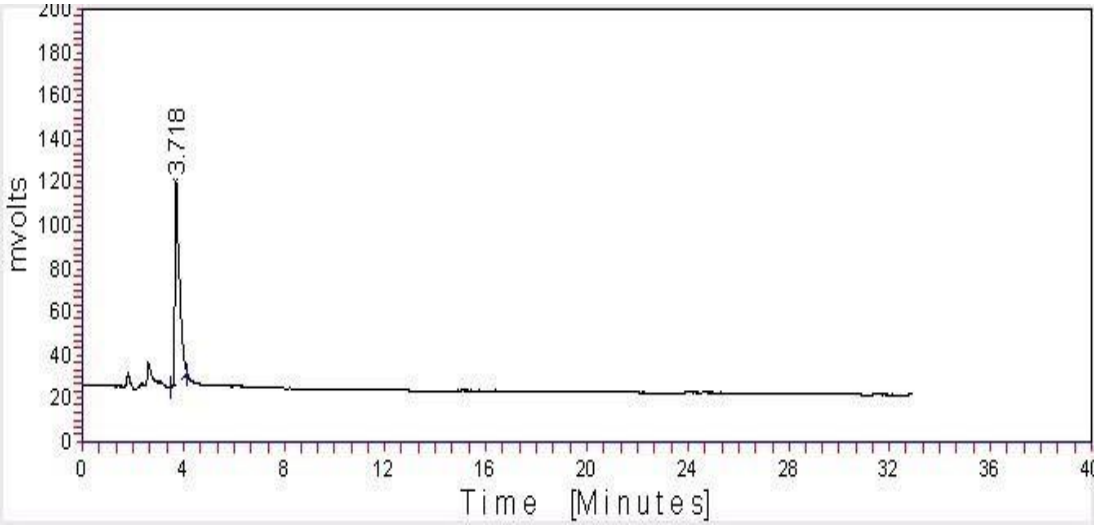

Figure 11: Graph of Analysis of Tablet Sample

The RP-HPLC method was developed for estimation of Ziprasidone in bulk and capsule dosage form by isocratically using Methanol: Acetonitrile in the ratio of 50:50 v/v as mobile phase, Thermo C-18 column (4.6 x 250mm, 5µparticle size) column as stationary phase and chromatogram was recorded at 250 nm. Then developed method was validated by using various parameters.

System suitability

The system suitability parameter was carried out to verify that the analytical system was working properly and could give accurate and precise result. The six replicates of reference standard, 10 µg/ml of Ziprasidone were injected separately and chromatogram was recorded. The result of system suitability parameter is reported in table.

Table 18: Results of system suitability parameters

Parameters	**Ziprasidone**
No. of Theoretical Plates	3553.33
Tailing Factor	0.955
Retention time	3.989±0.001

Linearity

The linearity of analytical method was carried out to check its ability to elicit test results that are proportional to the concentration of analyte in sample within a given range. Different levels of standard solutions were prepared and injected into the HPLC and the chromatogram was recorded. The results of linearity are reported in table

Table 19: Results of linearity of Ziprasidone

Parameter	**Ziprasidone**
Conentration(µg/ml)	5-25
Correlation Coefficient (r^2)*	0.999
Slope (m)*	61.43
Intercept (c)*	-1.745

*value of five replicate

Specificity

Specificity of the method was determined and the peaks of diluent, mobile phase and excipient of tablets did not interfere with standard peaks Ziprasidone.

Accuracy

The validity and reliability of proposed methods were assessed by recovery studies. The recovery of added standards (80%, 100% and 120%) was found at three replicate and three concentrations level. The value of % means just close to 100, SD and % RSD are less then 2 indicate the accuracy of method. Result of recovery study shown in table.

Table 20: Results of recovery study

% LEVEL	**% MEAN±SD***
	Ziprasidone
80%	99.62±0.084
100%	99.71±0.091
120%	99.78±0.170

***** Value of three replicate and three concentrations.

Precision

Precision was determined by repeatability and Intermediate precision of drug. Repeatability result indicates the precision under the same operating condition over short interval time. The intermediate precision study is expressed within laboratory variation on different days and analyst to analyst variation by different analyst. The value of SD and %RSD are less then 2 indicate the precision of method. Result of precision shown in table.

Table 21: Results of Precision

Parameter	% MEAN±SD*
	Ziprasidone
Repeatability	99.739±0.028
Intermediate precision	
Day to day precision	99.276 ±0.041

***** Value of five replicate and five concentrations

Robustness

The robustness of developed method was checked by changing in the deliberate variation in solvent. Result of robustness shown in table.

Table 22: Results of robustness

PARAMETER	% MEAN±SD*
	Ziprasidone
Robustness	99.458±0.065

*Value of five replicate and five concentrations

LOD AND LOQ

Detection limit and quantitation limit of described method were observed as 0.095

µg/ml, and 0.271 µg/ml respectively based on the SD of response and slope, which meet the requirement of new method.

Assay of tablet formulation

The results of the analysis of tablet formulation were reported. The assay value of drugs was close to 100, SD and % RSD are less then 2 indicate the no interference of excipient in the estimation of drugs.

Table 23: Assay of tablet formulation

S. No.	Parameter	Ziprasidone
1.	Mean	99.98
2.	S. D.	0.125
3.	% RSD	0.145

SUMMARY AND CONCLUSION

In the present research work, a successful attempt was made for "Method Development and Validation for Estimation of Ziprasidone in marketed formulation by using RP-HPLC" which was developed by experimentation based on thorough literature survey and ascertained by statistical parameters of sampling. The simplicity, rapidity, accurate and reproducibility of the proposed methods completely fulfill the objective of the research work of estimation of the drug in marketed formulation. Proposed method was found to be linear in the range of 5-25 µg/ml Ziprasidone with the correlation coefficient near to one respectively. The validation and the reliability of proposed method were assessed by recovery study. The recovery of added standards (80%, 100% 120%) was ranging from 99.62 to 99.784%, for Ziprasidone. Liquid chromatographic system from waters comprising of manual injector, Waters 515 binary pump for constant flow and constant pressure delivery and U.V. detector connected to data ace software controlling the instrumentation as well as processing methanol: Acetonitrile in the ratio of 50:50 v/v at a flow rate of 1.0 ml min^{-1}. A thermo C-18 column (4.6 x 250mm, 5µ particle size) was used as the stationary phase, 250.0 nm was selected as the detection wavelength for UV-vis. detector. The proposed methods were found to be linear in the range of 5-25 µg/ml with correlation coefficient close to one. Precision was determined by repeatability, Intermediate precision and reproducibility of the drugs. The robustness of developed method was checked by changing in the deliberate variation in solvent. The result obtained shows the developed methods to be Cost effective, Rapid (Short retention time), Simple, Accurate (the value of SD and %RSD less than 2), Precise and can be successfully employed in the routine analysis of these drugs in bulk drug as well as in tablet dosage form. The Simplicity, Rapidly and Reproducibility of the proposed method completely fulfill the objective of this research work.

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