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DEVELOPMENT AND VALIDATION OF PALIPERIDONE IN BULK AND PHARMACEUTICAL FORMULATION BY UV SPECTROSCOPY

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Abstract: A simple, precise and economical Zero-order Spectroscopy (Method A), Area Under Curve [AUC] (Method B) UV-Spectrophotometric methods have been developed and validated for the estimation of Paliperidone in bulk and its formulation. The solutions of standard and sample were prepared using 0.1N HCl. Paliperidone was estimated at 238 nm for the zero order and, AUC of Paliperidone was measured in between 232-244 nm. Beer's law was obeyed in the concentration range of 3-18 µg / ml with r^2 value 0.9998, 0.999 for Zero order method and AUC spectroscopy. The precision expressed as relative standard deviation, which was within 2.0 % for the above three methods. The proposed methods were successfully applied for the determination of Paliperidone in bulk and pharmaceutical formulations. In addition, the proposed methods are simple, easy to apply, low-cost, and requires relatively inexpensive instruments.

Keywords: Paliperidone; Method validation; Zero order derivative; AUC, UV-Spectroscopic methods.

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INTRODUCTION

Paliperidone (*RS*)-3-[2-[4-(6-fluorobenzo[*d*]isoxazol-3-yl)-1-piperidyl]ethyl]-7-hydroxy-4-methyl-1,5-diazabicyclo[4.4.0]deca-3,5-dien-2-one (Figure 1) is a dopamine antagonist of the atypical antipsychotic class of medications. It is a long lasting injectable formulation and Invega is an extended release formulation. Paliperidone is used to treat mania, schizophrenia, schizoaffective disorder and at lower doses as maintenance for bipolar disorder. It is not official in Indian Pharmacopoeia. Few analytical methods were appeared in the literature survey for the determination of Paliperidone, which includes HPTLC, HPLC and LC-MS/MS with human plasma but there are no reported spectrophotometric methods[1]. In view of above fact, some simple and analytical methods were planned to develop with sensitivity, accuracy, precision and economical[2]. In the present investigation, three simple and sensitive UV spectrophotometric methods were developed for the quantitative estimation of Paliperidone in bulk drug and pharmaceutical formulations[3].

MATERIALS AND METHODS

A Shimadzu-1800 UV / Vis double beam Spectrophotometer with 1 cm matched quartz cells was used for all spectral measurements. All chemicals used were of A.R. grade from S.D.Fine-chem, Merck, Fischer scientific, and Spectrochem, Mumbai. Authentic drug sample of Paliperidone was given as a gift sample by Microlabs Pvt limited, Bangalore. Tablets of Paliperidone were procured from local market.

METHOD A:

ZERO ORDER DERIVATIVE SPECTROSCOPY FOR DETERMINATION OF PALIPERIDONE USING 0.1 N HCL

Method A is UV-Spectrophotometric method which involves the determination of Paliperidone in bulk drug and pharmaceutical formulations and has an absorption maximum at 238 nm in 0.1N HCl. It obeys Beer's law in the concentration range of 3-18 µg / ml.

Method Development

Preparation of Standard Stock Solution

Standard stock solution was prepared by dissolving accurately weighed 100 mg of Paliperidone in 0.1N HCl and the volume was made up to 100 ml with 0.1N HCl in 100 ml volumetric flask (Stock solution-I, 1000 mcg / ml). 10 ml of stock solution-I was diluted to 100 ml with 0.1N HCl (Stock solution-II, 100 mcg / ml). 1 ml of stock solution-II was taken in 10 ml standard flask diluted to 10 ml with 0.1N HCl to get the concentration 10 µg / ml The absorbance of resulting solution was measured against respective blank solution in the UV region of 200-400 nm, which shows maximum absorbance at 238nm (Figure 2).

Preparation of Standard Curve:

Appropriate volume of aliquots from standard Paliperidone stock solutions were transferred to a series of 10 ml volumetric flasks capacity. The volume was adjusted to the mark with 0.1N HCl to obtain concentrations of 3 to 18 µg / ml absorbance spectra of each solution against 0.1N HCl as a blank were measured at 238 nm and the absorbance values (Table 1). The obtained absorbance values are plotted against the concentration of Paliperidone to get the calibration graph (Figure 3). The regression equation and correlation coefficient was determined (Table 2).

Sample Preparation of Paliperidone:

Twenty tablets of Paliperidone were taken, make fine powder of the tablet and the powder equivalent to 100 mg of Paliperidone was weighed accurately and transferred into a 100 ml standard volumetric flask. The contents were dissolved in 0.1N HCl and sonicated for 30 minutes. This entire solution was filtered through 0.45 micron Whatmann filter paper (No. 41) and the final solution was made with 0.1N HCl to get the solution of 1000 µg / ml. From this solution, 10 ml was taken in 100ml standard volumetric flask and diluted to 100ml with 0.1N HCl to get the solution of 100 µg / ml. An aliquot of 0.3 ml – 1.8 ml of test solution was diluted to 10 ml with Paliperidone in 10 ml standard volumetric flask to produce the concentration range of 3 µg / ml to 18 µg / ml.

METHOD B: AREA UNDER CURVE

Method B is Area under curve Spectrophotometric method which involves the determination of Paliperidone in bulk drug and pharmaceutical formulations and has absorption at 232 to 244nm 0.1N HCl (Figure 4). It obeys Beer's law in the concentration range of 3-18 µg / ml.

Method Development

Preparation of Standard Stock Solution

The Standard stock solution of Paliperidone was prepared same as described in method A. The absorbance of resulting solution was measured against 0.1N HCl as a blank solution in the UV region of 200-400 nm, which shows area at 232 to 244 nm.

Preparation of Standard Curve

Aliquots of standard solution of Paliperidone were prepared same as described in method A. The area was measured at 232 to 244nm against blank and the absorbance values (Table 6). The obtained area values when plotted against the concentration of Paliperidone gives the calibration graph (Figure 5). The regression equation and correlation coefficient (Table 7).

Sample Preparation of Paliperidone:

The Sample preparation of Paliperidone was prepared same as described in Method A. From the finial stock solution, various dilutions of sample solution were prepared and analyzed.

UV-SPECTROPHOTOMETRY

UV Spectrophotometry was divided in to three Methods.

Method A: Zero Order Derivative Spectroscopy

Method B: Area Under Curve Spectroscopy

The absorption spectra were recorded in the wavelength region of 200-400 nm in UV method (Figures 2 & 3)[4,5].

RESULTS AND DISCUSSION

Optimum Conditions, Optical Characteristics and Statistical Data of the Regression Equation in UV Method

The optical characteristics such as Beer's law limits, Molar absorptivity, Sandell's sensitivity, Limit of detection and Limit of quantitation etc., in each method were calculated (Tables 2 & 7). Also the regression characteristics like slope (b), intercept (a), and correlation coefficient (r2) using the method of least squares were calculated (Tables 2 & 7. The results showed that the methods have reasonable precise.

Recovery Studies

Results obtained with proposed methods confirm the suitability of these methods for pharmaceutical dosage forms. The accuracy of the methods were confirmed by the recovery studies, by adding known amount of the pure drug to the pharmaceutical formulation and the percentage recovery studies were determined (Tables 3 & 8). The results were within the range of were found to be highly accurate.

Interference Studies

The Interference studies were carried out to the excipients present in the dosage form of Paliperidone. Excipients did not interfere, when estimated by the proposed methods. The reported methods were found to be simple, sensitive, accurate, precise, and economical and can be used in the determination of Paliperidone in pharmaceutical formulation.

Precision

The precision of an analytical method was calculated by performing intra-day precision and inter-day precision studies. The values were found to be precise (Tables 4 & 9).

Linearity

The linearity was found in the concentration range of 3-18 µg / ml for Zero order derivative spectroscopy &Area under curve. The correlation coefficients were found to be 0.9998 & 0.9996 respectively. The obtained (r2) values show that the selected concentration range gives good linearity.

Ruggedness

The ruggedness studies were performed by the two analysts for the dosage form. The % recoveries were calculated (Table 5 & 10). The values were between the ranges and these values were found to be within the limit and method is found to be rugged.

CONCLUSION

For routine analytical purpose, it is always necessary to establish methods capable of analyzing huge number of samples in a short time period with due accuracy and precision. Two simple and sensitive UV spectrophotometric methods were developed for the quantitative estimation of Paliperidone in bulk drug and pharmaceutical formulation. In addition to positive requirements of these analytical methods, the striking advantage of all the presently developed methods was that they were economical.

The results of Zero order and Area under curve spectroscopic methods, were found to be good (Tables 1-10). The methods were validated in terms of linearity, accuracy, precision, and ruggedness and used for the routine determination of Paliperidone in bulk drug and in pharmaceutical formulation.

FIGURES

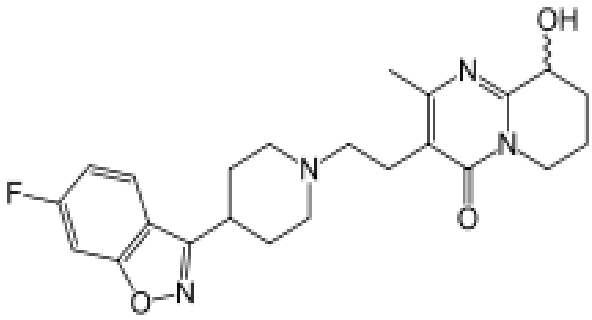

Figure 1: Structure of Paliperidone

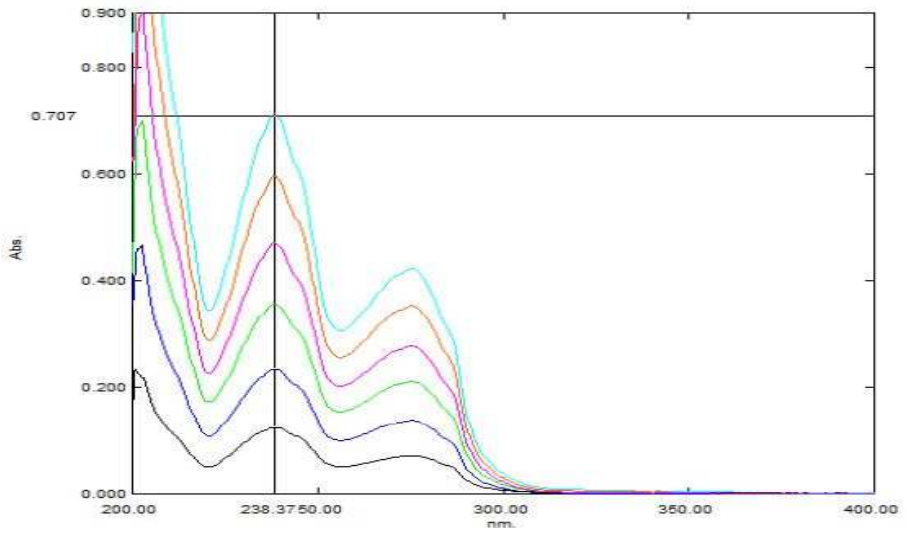

Figure 2: Zero order spectra of Paliperidone at 238nm

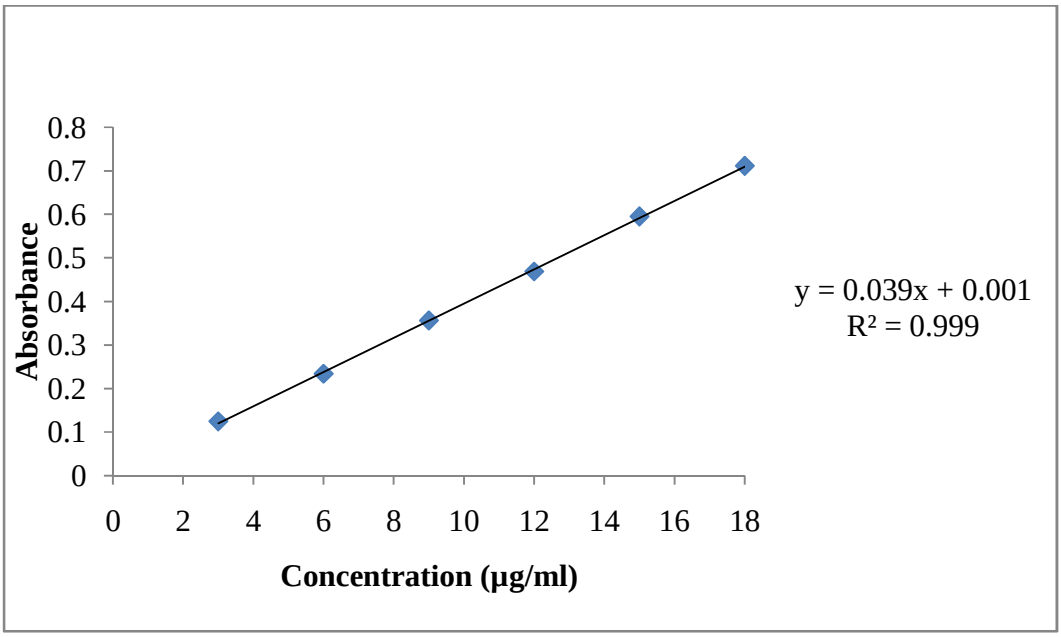

Figure 3: Calibration curve of Zero order Spectroscopy of Paliperidone

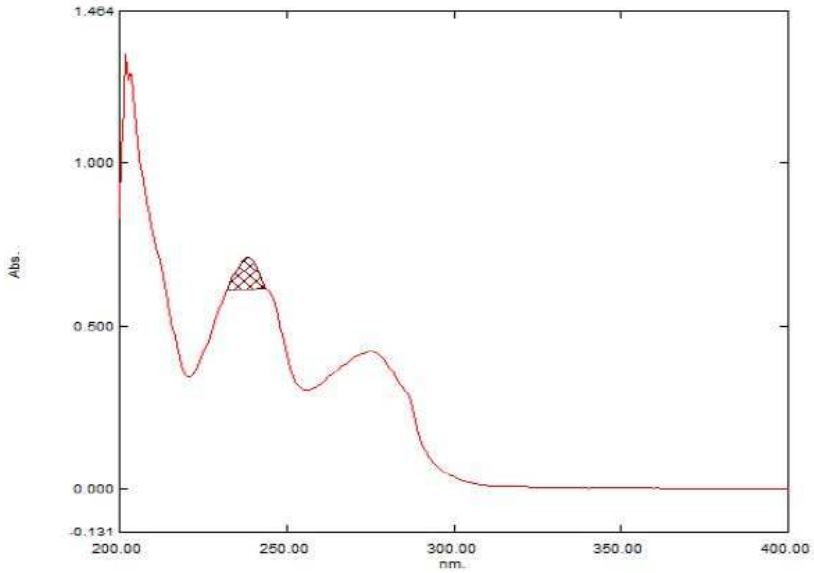

Figure 4: Area under curve spe ctra of Paliperidone at 232 to 244nm

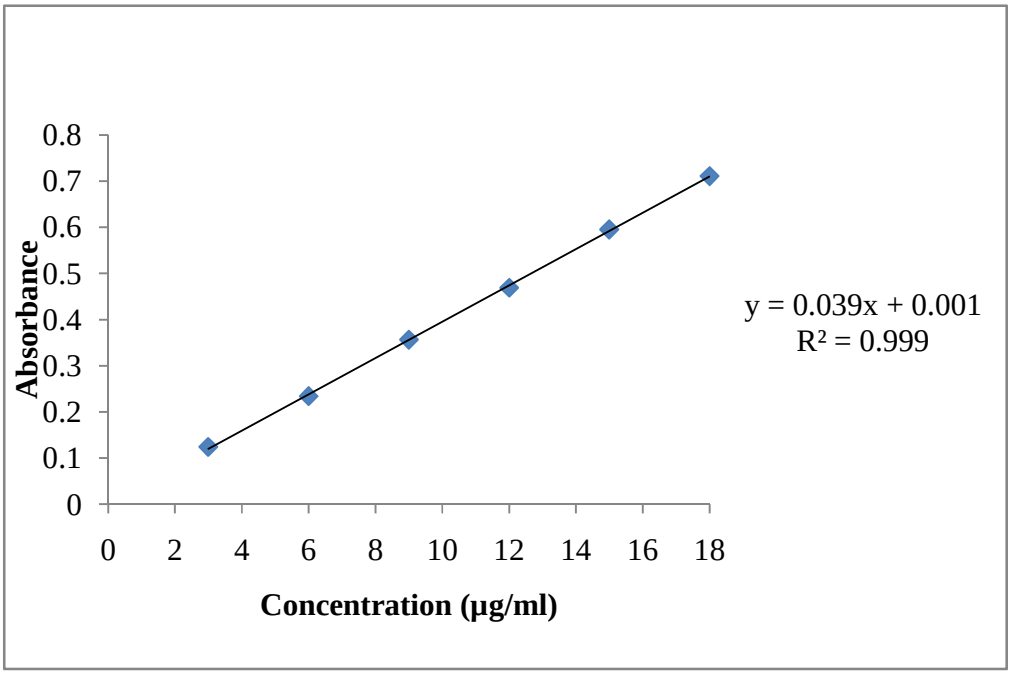

Figure 5: Calibration curve of Zero order Spectroscopy of Paliperidone

Table 1

Results of calibration curve at 238 nm

Si. No.	Conc (µg/ml)	Absorbance at 253
1	3	0.124
2	6	0.234
3	9	0.356
4	12	0.469
5	15	0.595
6	18	0.711

Table 2

Optimum conditions, Optical characteristics and Statistical data of the Regression equation in Zero order Spectroscopy

Parameter	UV method
λ_{max} (nm)	238
Beer's law limits (µg/ml)	3-18
Molar extinction coefficient (L mol^{-1} cm^{-1})	0.039 × 10^4
Sandell's sensitivity (g/cm^2 -0.001 absorbance units)	0.025281
Regression equation (Y*)	Y=0.0394x+0.0009
Slope (b)	0.0394
Intercept (a)	0.0009
Correlation coefficient (r^2)	0.9998
Intraday Precision (%RSD**)	0.211
Interday Precision (%RSD**)	0.251
Limit of detection (µg/ml)	0.043
Limit of quantitation (µg/ml)	0.132

*Y = bx+a where x is the concentration of Paliperidone in **µg/ml** and Y is the absorbance at the respective λ_{max}

** Average of Six determinations.

Table 3

Determination of Accuracy results for Paliperidone at 238 nm by Zero order Spectroscopy

Brand used	Amount of drug added (µg / ml)	Amount of sample added (µg / ml)	Amount Recovered	% Recovery ± SD**
Paliperidone	6	3	9.035	100.39±0.63
	6	6	11.929	99.41±0.94
	6	9	15.035	100.23±0.37

Table 4

Determination of Precision results for Paliperidone at 238nm by Zero order Spectroscopy

Conc. (µg / ml)	Intra-day Absorbance Mean ± SD	% CV	Inter-day Absorbance Mean ± SD**	% CV
3	0.1238±0.00075	0.60	0.124±0.00109	0.88
6	0.2338±0.00075	0.32	0.233±0.00089	0.38
9	0.3561±0.00075	0.21	0.356±0.00089	0.25
12	0.4683±0.0081	0.17	0.468±0.00089	0.19
15	0.595±0.00126	0.21	0.595±0.00116	0.19
18	0.7125±0.001871	0.26	0.712±0.00066	0.09

**Average of Six determinations

Table 5

Ruggedness results for Paliperidone at 238nm by Zero order Spectroscopy

Brand used	Label claim (mg)	Analyst I		Analyst II	
		Amount found** (mg)	% Recovery ± SD**	Amount found** (mg)	% Recovery ± SD**
Paliperidone	3	3.010	100.39±0.63	2.98	99.41±0.94

**Average of six determinations.

Table 6

Results of calibration curve at 232 to 244nm for Paliperidone by Area under curve Spectroscopy

Si. No.	Conc (µg/ml)	Area
1	3	0.127
2	6	0.228
3	9	0.339
4	12	0.449
5	15	0.568
6	18	0.678

Table 7

Optimum conditions, Optical characteristics and Statistical data of the Regression equation in Area under curve Spectroscopy

Parameter	UV method
λ_{max} (nm)	232-244
Beer's law limits (µg/ml)	3-18
Molar extinction coefficient (L mol^{-1} cm^{-1})	0.037 × 10^4
Sandell's sensitivity (g/cm^2 -0.001 absorbance units)	
Regression equation (Y*)	0.026549
	Y=0.0373x+0.0052
Slope (b)	0.0373
Intercept (a)	0.005
Correlation coefficient (r^2)	0.9996
Intraday Precision (%RSD**)	0.221
Interday Precision (%RSD**)	0.263
Limit of detection (µg/ml)	0.045
Limit of quantitation (µg/ml)	0.139

*Y = bx + a where x is the concentration of Paliperidone in µg / ml and Y is the absorbance at the respective λmax . **Average of Six determinations

Table 8

Determination of Accuracy results for Paliperidone at 232 to 244nm by Area under Curve Spectroscopy

Brand used	Amount of drug added (µg / ml)	Amount of sample added (µg / ml)	Amount Recovered	% Recovery ± SD**
Paliperidone	6	3	9.037	100.41±0.079
	6	6	11.925	99.38±0.119
	6	9	15.037	100.24±0.47

Table 9

Determination of Precision results for Paliperidone at 232 to 244nm by Area under Curve Spectroscopy

Conc. (µg / ml)	Intra-day Absorbance Mean ± SD	% CV	Inter-day Absorbance Mean ± SD**	% CV
3	0.1268±0.00075	0.59	0.127±0.00109	0.86
6	0.2278±0.00075	0.33	0.227±0.00089	0.39
9	0.3391±0.00075	0.22	0.339±0.00089	0.26
12	0.4483±0.0081	0.18	0.448±0.00089	0.19
15	0.568±0.00126	0.22	0.568±0.00116	0.20
18	0.6795±0.00187	0.27	0.679±0.00066	0.09

**Average of Six determinations

Table 10

Ruggedness results for Paliperidone at 232 to 244nm by Area under curve Spectroscopy

Brand used	Label claim (mg)	Analyst I		Analyst II	
		Amount found** (mg)	% Recovery ± SD**	Amount found** (mg)	% Recovery ± SD**
Paliperidone	3	3.010	100.41±0.79	2.980	99.38±0.119

**Average of six determinations.

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