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Research Article

Analytical methods for the estimation of paliperidone

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ABSTRACT

Four simple, sensitive, rapid and accurate analytical methods have been developed for the estimation of paliperidone in bulk and pharmaceutical dosage forms. Paliperidone is an atypical antipsychotic. Methnd I was a precise reverse phase HPLC involving an isocratic elution of Paliperidone in a column of *Pkenomenex CIS,* using a mobile phase composition of acetonitrile: Methanol: Potassium dihydrogen phosphate (45:30:25, v/v). The flow rate was 1.0 ml/min and the effluent was monitored at 275 nm and retention time was observed at 4.15 mm. Forced degradation studies were carried out in acid and basic medium, oxidative degradation in H2O2 and as well as uv photo stability studies. Methnd H *&* HI are visible spectrophotometnc methods based on the formation of red colored complex between Paliperidone and PDACA which showed linearity in the concentration range 20-120 |ig/ml and between Paliperidone and 4-Amino phenazone in red colored chromogen which obeyed Beer's law 30-150 |ig/ml at absorbance maxima of 460 nm and 532 nm respectively Method IV was a simple ultraviolet spectroscopic method was developed for the estimation of Paliperidone in 0.1N HC1 which obeyed Beer's law in the linearity range 5-25 |ig/ml at 275 nm. The proposed methods are optimized and validated as per the ICH guidelines. Recovery of paliperidone in the proposed methods was found to be in the range of 97.5-99.2 %. The proposed methods can be used for routine analysis for the estimation of paliperidone in formulations.

Keywords: Paliperidone; HPLC, UV Visible spectrophotometry.

INTRODUCTION

Chemically, paliperidone (Moody DE et al., 2004) is the primary active metabolite of the older atypical antipsychotic risperidone. Paliperidone is 9-hydroxyrisperidone. It is ((*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. It is indicated for the acute and maintenance treatment of schizophrenia. Specific mechanism is not known. Its therapeutic effect may be due to a combination of D_2 and 5-HT receptor antagonism. Paliperidone has an antagonist effect at α_1 and α_2 adrenergic receptors and H_1 histamine receptors. Review of the scientific literature showed that Paliperidone was mainly assayed by a HPTLC (Rashmin B P et al., 2010), HPLC (Bladania SL et al., 2008; Danel C et al., 2007; El-Sherif ZA et al., 2005) and a RP-RRLC (Andhariya J V et al., 2009) method. Since no other analytical method was reported four methods were developed for the estimation of paliperidone in routine analysis.

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MATERIALS

The chromatographic instrument consisted of a low pressure gradient HPLC pump, a UV variable detector from Shimadzu. The data was acquired and processed by means of Spinchrom CFR-2.3.0.149 chromatography software. A Jasco- V530 spectrophotometer and Shimadzu UV-17OO spectrophotometer with 10mm matched quartz cell was used for spectroscopic measurements. HPLC grade solvents obtained from merck was used for HPLC studies and analytical grade solvents were used for UV Visible spectrophotometric studies.

METHOD 1 (M1)

A simple, precise and accurate RP-HPLC method was developed for the estimation of Paliperidone in bulk and dosage forms. The stock solution of paliperidone was prepared by weighing accurately about 100mg of pure drug in100ml of Acetonitrile. The stock solution was further suitably diluted. Into 5 volumetric flask of strength 10 ml, 1to5 ml of working standard solution of paliperidone was added and made up to the mark with solvent system. The parameters like flow rate, LOD, LOQ, mobile phase ratio were optimize to get better resolution, precision and accuracy. Successive aliquots of standard solution were injected into the chromatographic system. The linearity concentration range selected was from 100-500 µg/ml. These standard solutions were injected into the fixed chromatographic conditions and chromatograms were obtained at 275 nm.

CHROMATOGRAPHIC CONDITION

Mobile Phase Buffer (45:30:25,v/v)	:	ACN: Methanol:
Analytical column 250 x 4.6mm, 5µ.	:	Phenomenex, C18,
Column Temperature	:	28°c
λmax	:	275nm.
Flow rate	:	1ml / min.
Injection Volume	:	20 µL
Run Time	:	10 minutes
Retention Time	:	4.150 min.
Range	:	0.0100 AUFS
Operation Pressure	:	2000-2500 Kgf

Table 1: Validation and system suitability studies of method 1

Parameter	Results
Retention time (min)	4.15
Asymmetry peak (10%)	1.15
Theoretical plates	3060.71
Capacity factor	33.58
Linearity range (µg/ml)	100-500
Correlation coefficient	0.9997
%RSD	0.5099

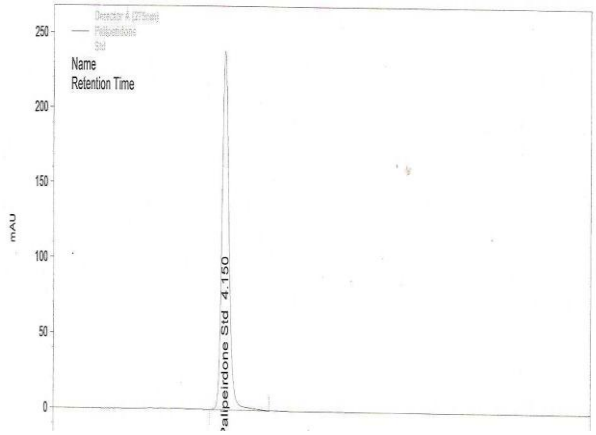

Figure 1:

METHOD 2 (M2)

Stock solution of Paliperidone was prepared by weighing accurately 50mg of pure drug in to a 50ml volumetric flask, and then dissolved in to 25ml of 0.1N HCl and make up to mark with 0.1N HCl. Aliquots of Paliperidone working standard solution were taken into calibrated 10 ml volumetric flask (20-120µg/ml), to this 1.5 ml of 0.7% PDACA was added and the reaction mixture was kept aside for 5 min, for the completion of reaction. The absorbances of the resulting red colored chromogens were measured at 460 nm against reagent blank within 2 hours.

METHOD 3 (M3)

Stock solution of Paliperidone was prepared by dissolving 100 mg of drug in 0.1N H_2SO_4 volume was made up to 100 ml with the same and working standard solution of Paliperidone was prepared by further diluting the stock solution suitably with 0.1N H_2SO_4 to get a working concentration of 100µg / ml. Aliquots of working standard solution ranging from 0.3-1.5 ml (30 -150 µg/ml) was taken into 10 ml volumetric flasks. To each of the flask 2 ml of 2% 4- Aminophenazone was added, followed by 1ml of 2% Potassium ferricyanide was added, followed by 1ml of 1% Sodium carbonate and allowed to stand for 5 min and made up to the mark with distill water and the absorbance of the red colored chromogens were measured at 532 nm against reagent blank with 90 min.

By postulating appropriate analogy the probable reaction taking place was condensation reaction in method 3 and method 4 resulting in the formation of red chromogen, which showed absorbance maxima at 460 and 532 nm shown in Fig2 & 3 respectively.

METHOD 4 (M4)

Stock solution was prepared as in method II using 0.1N HCl and further dilutions were prepared to get a working concentration of 100 µg/ml. Aliquots of the working standard solution of paliperidone (5-25µg/ml) were taken in calibrated 10 ml volumetric flasks and the volume was made up to the mark with distilled water. The absorbance of the resulting solutions was measured at 275 nm against the reagent blank.

All the proposed methods were extended to formulations and were optimized and validated as per the ICH guidelines.

RESULTS AND DISCUSSION

The developed methods which are described here have been validated for specificity, linearity, accuracy, precision, limit of detection, limit of quantification and solution stability. Detection limit for paliperidone was 500 ng/ml and quantification limit was 1µg/ml by HPLC method.

The system suitability was determined by six replicate injections from freshly prepared standard solutions for their peak area, theoretical plates (N) and peak asymmetry factors were calculated in the present study in Table 1.

Precision of the method was demonstrated by repeatability studies. Repeatability studies were done by consequently injecting the standard solution, containing 500µg/ml of Paliperidone six times and passing them through the assay procedure. Mean response was calculated followed by calculation of relative standard deviation.

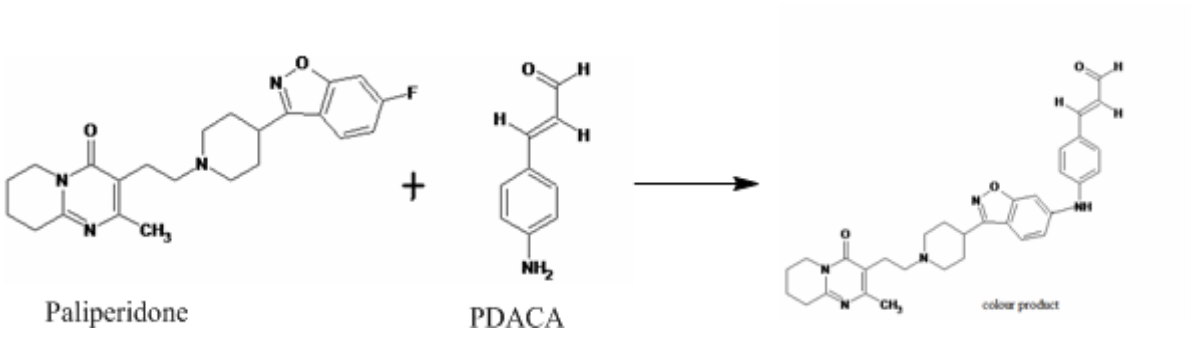

Figure 2:

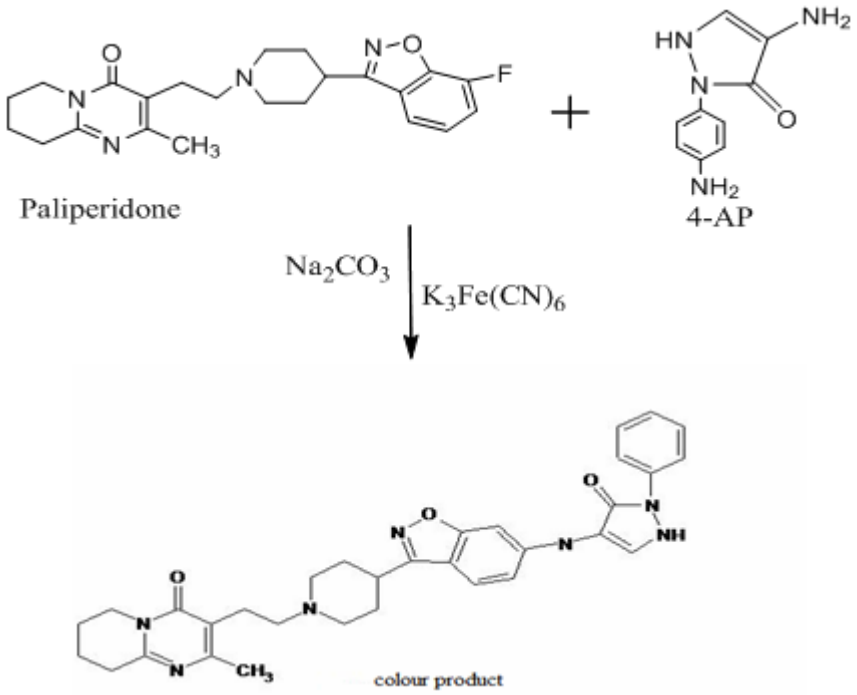

Figure 3:

Table 2: %Recovery of the proposed methods

Formulation	Labelled amt(mg)	Amt obtained(mg)				% recovery			
		M1	M2	M3	M4	M1	M2	M3	M4
Palido	**3 mg**	2.88	2. 90	2.85	2.94	96.33	96.81	95.15	98.13
Paliris	**9 mg**	8.87	8. 85	8.92	8.77	98.62	97.45	99.18	98.41

Table 3: Optical characteristic and precision of the proposed UV-VIS methods

SL. No.	Parameter	Method II	Method III	Method IV
1.	λ max (nm)	460.0	532.0	275.0
2.	Beer's law limits (µg/ml)	20-120	30-150	5-25
3.	Molar absorptivity (1/mol.cm)	$2.657x10^3$	$2.5116x10^3$	$9.0804x10^3$
4.	Sandell's sensitivity (µg.cm^{-2}/0.001/Au)	0.1463	0.1547	
5.	Regression equation (y = ax+b) Slope (b) Intercept (a)	 0.007 0.0263	 0.007 0.162	 0.024 0.006
6.	Correlation coefficient (r)	0.9997	0.9997	0.9998
7.	Relative standard deviation (%)	0.2689	0.1993	1.3423
8.	% Range of error (confidence limit) 0.01 level 0.05 level	 0.2248 0.3326	 0.1666 0.2465	 1.1224 1.6605

Accuracy of the proposed method was established by recovery. The data are presented in tables II & III.

Forced degradation studies were carried out in acid and basic medium, oxidative degradation in H_2O_2 and as well as UV photostability studies. For acid base degradation powdered paliperidone tablet samples were kept in 0.1 N H_2SO_4 and 0.1N NaOH respectively for 24 hours and also exposed to ultraviolet light at 275 for 24 hours. The sample degraded to some extent in all the parameters tested except in UV a photo stability study was 91% recovery.

Percentage recovery showed that the proposed methods are free of interference of the excipients used in the formulation and all results obtained are reproducible with coefficient of variance less than 1%. The linear regression of absorbance on concentration with a correlation coefficient (r) of almost 1 indicates a good linearity between absorbance and concentration .The value of percentage relative standard deviation less than 1% and low percentage range of error confirm the high degree of precision and accuracy of the proposed method. The percentage recovery value, which is close to100%, indicates the reproducibility of the method and the absence of the excipients present in the formulation.

Recovery of paliperidone in the proposed methods was found to be in the range of 97.5-99.2 %.

CONCLUSION

The proposed methods can be used for routine analysis for the estimation of paliperidone in formulations.

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