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A Validated Spectrophotometric Method for Determination of Paliperidone Palmitate in Bulk Drug and its Pharmaceutical Dosage Form.

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ABSTRACT

The present research describes simple, sensitive, rapid, accurate, precise and economical spectrophotometric method for determination of paliperidone palmitate in bulk and extended release injectable suspension formulation. The Paliperidone palmitate obtained spectrum was determined at 278 nm. The linearity was obtained in the concentration range of 15.6–50 µg/ml for Paliperidone palmitate. Interference due to placebo was not observed at 278 nm. The recovery and precision was well within the ICH (International conference on Harmonization) define criteria. The method was found to be simple and sensitive for the Paliperidone palmitate determination in injectable suspension dosage form. The results of analysis have been validated statistically and by recovery studies.

INTRODUCTION

Paliperidone palmitate is a new long-acting antipsychotic injection for the treatment of acute and maintenance therapy in schizophrenia. Paliperidone (9-hydroxyrisperidone) is the major active metabolite of risperidone and acts at dopamine D(2) and serotonin 5HT(2A) receptors. As with other atypical antipsychotic, it exhibits a high 5HT(2A):D(2)affinity ratio. It also has binding activity as an antagonist at $\alpha(1)$ and $\alpha(2)$ adrenergic receptors and H(1) histaminergic receptors, but has virtually no affinity for cholinergic receptors [1].

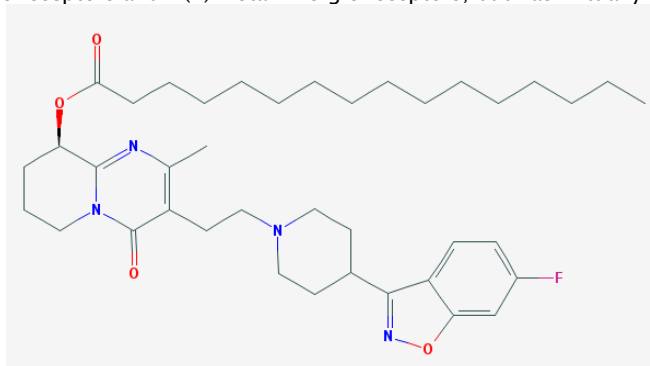


Figure 1: Chemical structure of Paliperidone palmitate

Intramuscular Paliperidone palmitate 39–234mg was generally well tolerated in adult patients with schizophrenia [2]. It offers several advantages over other available second-generation depotantipsychotics: it comes in prefilled syringes in a number of different dosages; it does not require refrigeration; it does not require supplementation with oral antipsychotic; it can be administered once monthly; it can be administered with a very small bore needle; the injection volume is small; the injection site can be either the deltoid or

gluteal muscles; and it does not require an additional precautionary observation period after the injection. For patients for whom oral risperidone or Paliperidone is otherwise effective, Paliperidone palmitate offers a guaranteed delivery system that enhances adherence [3]. High-performance liquid chromatography method is reported for the impurity determination of PP in active pharmaceutical formulation [4]. Science no spectrophotometric method is reported for estimation of PP in pharmaceutical dosage form therefore, in the present work, a successful attempt has been made to estimate PP by spectrophotometric method. The present manuscript describe simple, sensitive, rapid, accurate, precise and economical spectrophotometric method for the determination of Paliperidone palmitate in Paliperidone palmitate extended release injectable suspension.

MATERIALS AND METHODS

Apparatus

A double beam UV/Visible spectrophotometer (shimadzu model 1800, Japan) with spectral width of 2 nm, wavelength accuracy of 0.5 nm and a pair of 10 mm matched quartz cell was used to measure absorbance of all the solutions. Spectra were automatically obtained by UV-Probe system software.

Reagents and Materials

Paliperidone palmitate standards and samples were provided by Dr. Reddy's laboratories limited, IPDO, Hyderabad, India. Commercially available INVEGA SUSTENA (Paliperidone palmitate extended release injectable suspension). The HPLC-grade acetonitrile and tetrahydrofuran were purchased from Merck, Darmstadt, Germany. High purity water was generated using Milli-Q Plus water purification system (Millipore®, Milford, MA, USA).

Preparation of diluents

Mixture of acetonitrile and water in the ratio of 60:40 % v/v.

Preparation of standard solutions

An accurately weighed quantity of Paliperidone palmitate working standard (78 mg) was transferred in to a 250 ml volumetric flask. In above volumetric flask 60 ml of tetrahydrofuran was added and sonicated for 5 minutes and then diluted to volume with diluent, shake well. Transfer 5 mL of above solution in to 50 mL volumetric flask and diluted up to the mark with diluent, shake well (31.2 µg/ml).

Preparation of sample solutions

An accurately weighed quantity of Paliperidone palmitate suspension (approx 234 mg of sample suspension) was transferred in to a 250 ml volumetric flask. In above volumetric flask 60 ml of tetrahydrofuran was added and sonicated for 5 minutes and then diluted to volume with diluent, shake well. Transfer 5 mL of above solution in to 50 mL volumetric flask and diluted up to the mark with diluent, shake well.

Preparation of placebo solutions

An accurately weighed quantity of Paliperidone palmitate suspension (approx 234 mg of placebo solution) was transferred in to a 250 ml volumetric flask. In above volumetric flask 60 ml of tetrahydrofuran was added and sonicated for 5 minutes and then diluted to volume with diluent, shake well. Transfer 5 mL of above solution in to 50 mL volumetric flask and diluted up to the mark with diluent, shake well.

Methodology

The standard solutions of Paliperidone palmitate (31.2 µg/ml) was scanned separately in the UV range of 200–400 nm. The zero-order spectra thus obtained was then processed to obtain Paliperidone palmitate spectra. Data were recorded at an interval of 0.1 nm. The spectra was appeared that Paliperidone palmitate showed zerocrossing at 238 nm, 278 nm. Hence 278 nm was selected as analytical wavelengths for determination of Paliperidone palmitate. This wavelength can be employed for the determination of Paliperidone palmitate without any interference from the other excipients which are presented in the injectable suspension formulation.

Validation of the Proposed Method

The proposed method was validated according to the International Conference on Harmonization (ICH) guidelines ⁵.

Specificity

Specificity is the ability of the method to measure the analyte response in the presence of its placebo compounds. Diluent and formulation placebo interference was checked at 278 nm.

Linearity (Calibration curve)

The calibration curves were plotted over a concentration range of 15.6 to 50.0 µg/mL (15.6, 21.9, 31.2, 40.7 and 50.0 µg/ml) for Paliperidone palmitate. Absorbance was measured at 278nm for Paliperidone palmitate. The calibration curves were constructed by plotting absorbance versus concentration and the regression equations were calculated.

Method precision (repeatability)

The precision of this method was checked by scanning and measurement of absorbance of solution (six sets of sample preparations) for Paliperidone palmitate (31.2 µg/ml).

Intermediate precision (reproducibility)

The purpose of this study is to demonstrate the reliability of the test results with variations. The reproducibility was checked by analyzing the samples by different analyst using different system on different day. The analysis was conducted in the same manner as the method precision and the % RSD of all six sets of sample preparations was determined.

Accuracy (recovery study)

The accuracy of the method was determined by calculating recovery of Paliperidone palmitate of (31.2 µg/ml) by the standard addition method. Known amounts of standard solutions of Paliperidone palmitate was added to placebo at 50, 100 and 150 % level. The amounts of Paliperidone palmitate was estimated for three preparations of each level.

LOD and LOQ (Limit of detection and limit of quantification)

LOD and LOQ values are calculated based on PP spectral response.

RESULTS AND DISCUSSION

The standard solutions of Paliperidone palmitate scanned separately in the UV range, spectra (Figure 2) thus obtained. Data were recorded at an interval of 0.1 nm. The first spectra showed significance absorbance at 278 nm for Paliperidone palmitate (at 31.2 µg/mL). The spectra give good quantitative determination of the PP at 278 nm without any interference from drug placebo. Linear correlation was obtained between absorbance and concentration for Paliperidone palmitate (from 15.6µg/mL to 50µg/mL). Obtained linearity results are presented in Table 1.

Table 1: Regression analysis data and summary of validation parameters for the proposed method

Parameters	Results
Concentration Range (µg/ml)	15.6 µg/mL–50 µg/mL
Linearity (Equation)	$y = 0.0158x - 0.0031$
Correlation Coefficient (R ²)	0.9998
Precision (%RSD) (n = 6)	1.31 %
Intermediate precision (%RSD) (n = 6)	1.64 %
LOD	3.12 (µg/mL)
LOQ	9.36 (µg/mL)

Precision and intermediate precision study obtained values are presented in Table 1. The relative standard deviation (less than 2 %) indicates that the proposed method is repeatable. LOD and LOQ value for Paliperidone palmitate was found to be 3.12 µg/mL and 9.36 µg/mL, respectively (Table 1). These data show that proposed method is sensitive for the determination of Paliperidone palmitate. Recovery experiment results were presented in Table 2. The results of recovery studies indicate that the proposed method is accurate. Validated, developed method was applied for the determination of PP in commercially available dosage form. Obtained results (Table 3) indicated that the developed method is suitable for determination of PP in Pharmaceutical formulation. UV spectrums of Blank, Placebo, Standard and Sample solution are presented in Figure 2 to 5, which confirmed the stability indicating capability of developed method.

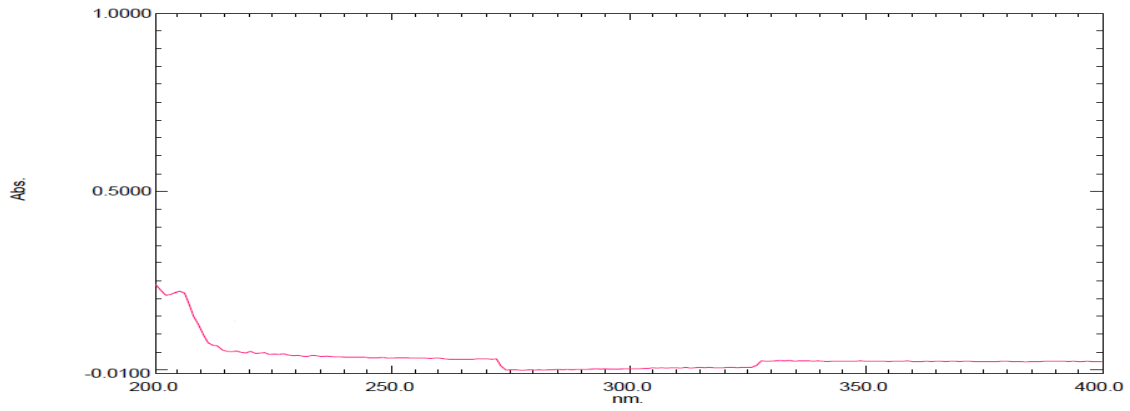


Figure 2: Blank UV spectrum

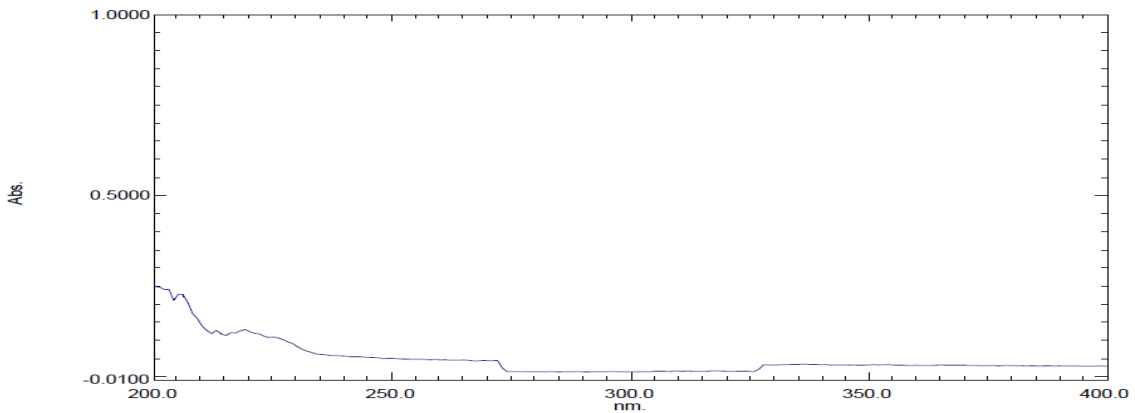


Figure 3: Placebo UV spectrum

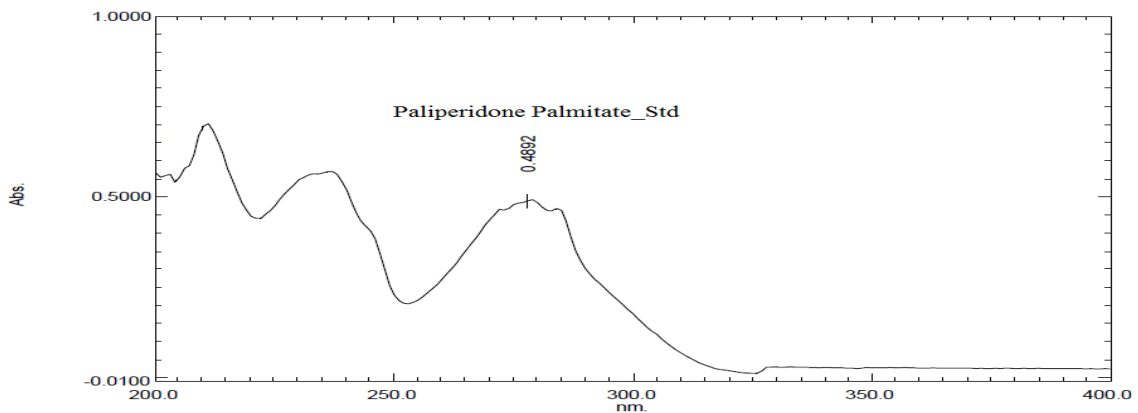


Figure 4: Standard UV spectrum

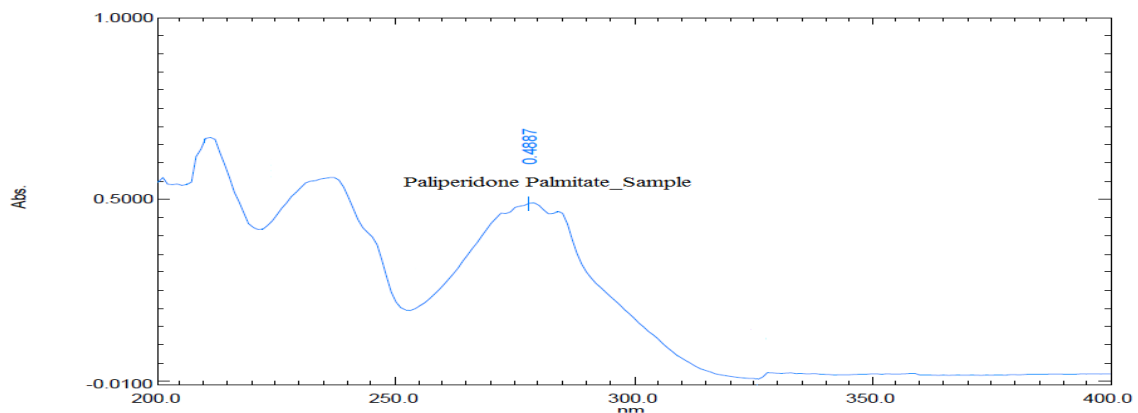


Figure 5: Sample UV spectrum

Table 2: Recovery data of proposed method

Drug	Level in %	Amount added ($\mu\text{g}/\text{mL}$)	% Recovery	% RSD
PP	50	15.6	98.87	1.57
	100	31.2	100.71	1.68
	150	50.0	100.92	1.72

Table 3: Results of market products

Product Name	Labeled claim (in mg)	Results obtained by developed method
INVEGA® SUSTENNA®	156 mg/mL	156.3 mg/mL

CONCLUSION

Based on the results, obtained from the analysis of described method, it can be concluded that the method has linear response in the range of 15.6–50 $\mu\text{g}/\text{ml}$ for Paliperidone palmitate. The result of the analysis of pharmaceutical formulation by the proposed method is highly reproducible and reliable and it is in good agreement with the label claim of the drug. This is also a cost effective method. Developed method can be used for the content uniformity test in Paliperidone palmitate extended release injectable suspension formulation. Developed method can be used for the quick determination of filling uniformity during filling of pre filled syringes, where sample load is higher and high throughput is essential for faster delivery of results.

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Authors' Statement

Competing Interests

The authors declare no conflict of interest.

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