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Spectrophotometric Determination of Ziparsidone Hydrochloride Using N-Bromosuccinimide and Metol

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Simple, accurate and reproducible UV-Visible spectrophotometric methods were established for the assay of ziparsidone hydrochloride (ZPD) based on the formation of oxidation and precipitation products. Method **A** involves the oxidation of the ZPD with N-bromo succinimide (NBS) and estimation of the unconsumed NBS with *p*-N-methyl aminophenol-sulphanilamide (PMAP-SA) reagent. Method **B** includes the estimation of unreacted NBS using a known excess celestine blue and the dye remaining was then measured. Quantitative precipitation of drug with tannic acid under acidic conditions and estimating the unreacted tannic acid in the filtrate with PMAP-Cr(VI) is proposed in method **C**.

Key Words: Spectrophotometry, Ziparsidone, Precipitation reagents.

INTRODUCTION

Ziparsidone[1] (as hydrochloride, ZPD) is used to treat psychotic disorders and symptoms such as hallucinations delusions and hostility. The FDA approved Geodon as a treatment for Schizophrenia in 2001. It helps manage Schizophrenia's "positive symptoms" such as visual and auditory hallucinations, delusions and thought disturbance. Geodon may also help in treating the 'negative symptoms' of Schizophrenia, which include social withdrawal apathy, lack of motivation and an inability to experience pleasure. Geodon is associated with little or no weight gain, a characteristic that distinguishes it from other antipsychotic drugs.

Few physico-chemical methods appeared in the literature for the assay of ZPD in biological fluids and pharmaceutical formulations. Most of them are based on visible spectrophotometric methods[2,3], HPLC[4-8], GC[9,10], fluorimetry[11-13]. LC-MS[14], GC-MS[15-17] and TLC[18], Mass[19]. Existing analytical methods reveal that relatively little attention was paid in developing visible spectrophotometric methods (only Folin Ciocalteu reagent was used) by exploiting the analytically useful functional groups in ZPD. Hence there is a need to develop sensitive and flexible visible spectrophotometric methods which prompted the author to carry out in this accord.

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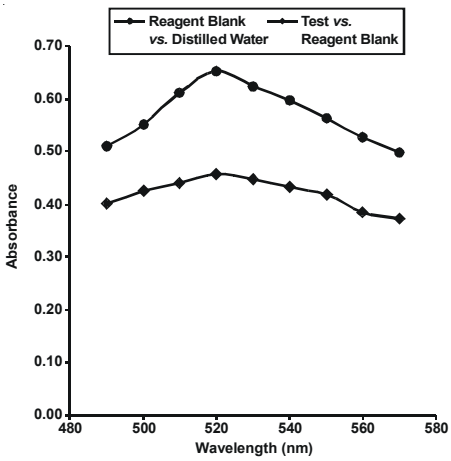
EXPERIMENTAL

An Elico, UV-Visible digital spectrophotometer with 1 cm matched quartz cells were used for the spectral and absorbance measurements. An Elico LI-120 digital pH meter was used for pH measurements.

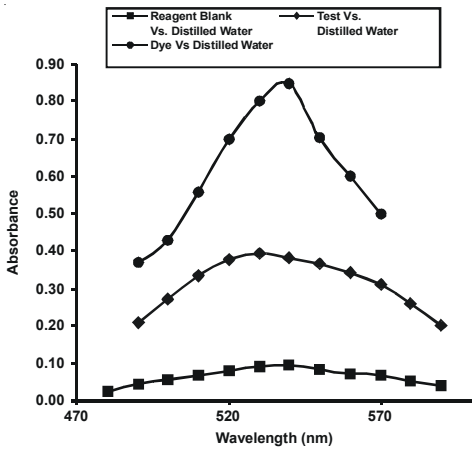
All the chemicals and reagents used were analytical grade and the aqueous solutions were freshly prepared with triple distilled water. A 1 mg/mL solution was prepared by dissolving 100 mg of pure ziparsidone hydrochloride (ZPD) in 100 mL of 0.1 N HCl and this stock solution was diluted step wise with distilled water to get the working standard solutions of required concentration. N-Bromo succinimide (NBS) (Loba; 0.088 %, 4.94×10^{-3} M), *p*-N-methyl amino phenol (PMAP) solution (0.3 %, 8.71×10^{-3} M) and sulphanilamide (SA) solution (S.D. Fine; 0.2 %, 1.16×10^{-2} M) for method **A**, NBS solution(Loba; 0.01 %, 5.618×10^{-4} M) celestine blue (CB) solution (Chroma; 0.005 %, 5.497×10^{-4} M) hydrochloric acid (E. Merck, 5 M) for method **B**, tannic acid (TA) solution (Loba, 0.2 %, 1.17×10^{-3} M); *p*-N-methyl aminophenol (PMAP) solution (Loba, 0.3 %, 8.71×10^{-3} M), Cr(VI) (BDH, 0.3 %, 1.01×10^{-2} M) and buffer solution (pH 3) were prepared for method **C**.

Recommended procedures

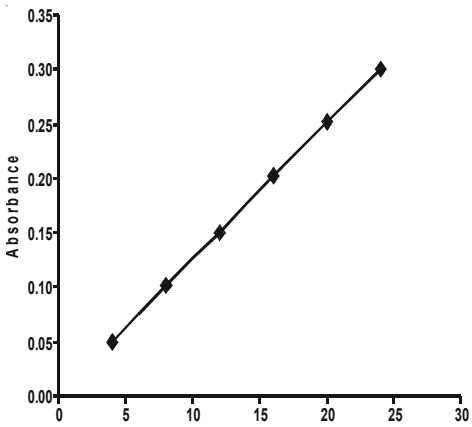
Method A: Aliquots of standard ZPD solution (1.0-5.0 mL, 200 μg mL^{-1}) were transferred into a series of 25 mL calibrated tubes. Then 0.5 mL (8.75×10^{-1} M) of AcOH and 2 mL (4.94×10^{-3} M) of NBS solutions were added and kept aside for 15 min at room temperature. Then 1.5 mL (8.71×10^{-3} M) of PMAP solution was added. After 2 min 2.0 mL (1.16×10^{-2} M) of sulphanilamide (SA) solution was added. The volume was made up to the mark with distilled water. The absorbance was measured after 10 min at 520 nm against distilled water. A blank experiment was also carried out omitting the drug. The decrease in the absorbance and in turn the drug concentration was obtained by subtracting the absorbance of the test solution from the blank. The amount of ZPD was computed from its calibration graph (Fig. 1).



Absorption spectrum of ZPD-NBS/PMAP-SA



Absorption spectrum of ZPD (NBS/CB) reagent



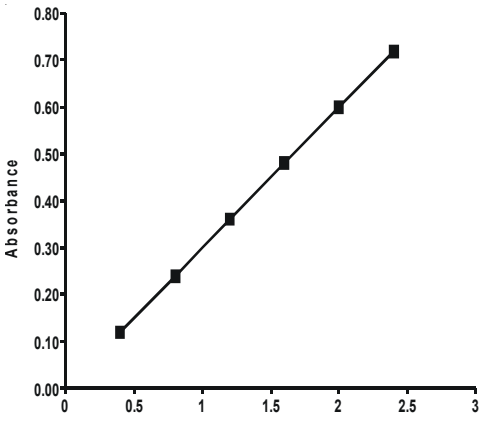


Fig. 1. Beer's law plot of ZPD-NBS/PMAP-SA Fig. 2. Beer's law plot of (ZPD-NBS/CB)

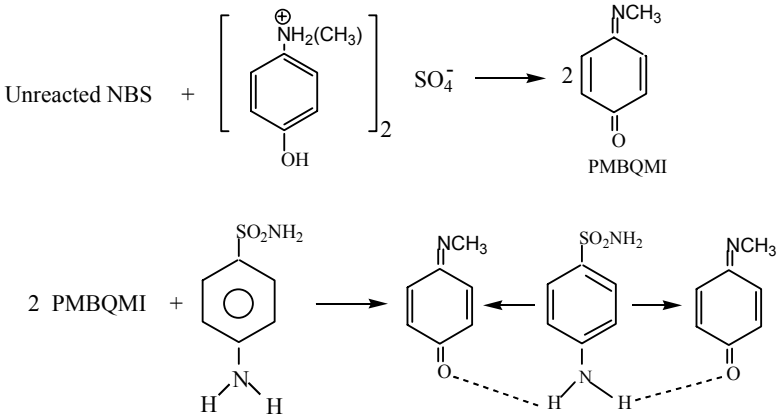
Method B: Aliquots of standard ZPD solution (0.5-3.0 mL, 20 µg mL^{-1}) were transferred into a series of 25 mL calibrated tubes. Then 1.25 mL (5.0 M) of HCl and 2.5 mL (5.618×10^{-4} M) of NBS were added. The volume was brought to 15 mL with distilled water. After 10 min, 10 mL (5.50×10^{-4} M) of CB solution was added and mixed thoroughly. The absorbance was measured after 5 min at 540 nm against distilled water. The blank (omitting drug) and dye (omitting drug and oxidant) solutions were prepared in a similar manner and their absorbances were measured against distilled water. The decrease in absorbance corresponding to consumed NBS and in turn the drug concentration was obtained by subtracting the decrease in absorbance of the test solution (dye-test) from that of the blank solution (dye-blank). The amount of ZPD was computed from its calibration graph.

Method C: Aliquots of standard drug solution (0.5-3.0 mL 400 µg/mL) were delivered in to a series of centrifuge tubes and the volume in each test tube was adjusted to 3.0 mL with 0.01 N HCl. Then 1.0 mL of tannic acid was added and centrifuged for 5 min. The precipitate was collected through filtration and subsequently washed with 2.0 mL of distilled water. The filtrate and washings were collected in a 25 mL graduated test tube. Then 15 mL of pH 3.0 buffer and 1.5 mL of PMAP solutions were successively added. After 2 min 2.0 mL of Cr(VI) solution was added and the volume was made up to the mark with distilled water. The absorbance was measured after 5 min at 560 nm against distilled water. A blank experiment was also carried out omitting the drug. The decrease in absorbance and in turn drug concentration was obtained by subtracting the absorbance of the test solution from the blank. The amount of drug was calculated from Beer's law plot (Fig. 2).

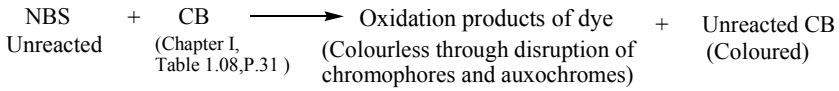
Methods A & B

Step I: ZPD + NBS → Oxidation products (s) of ZPD + Unreacted NBS (Excess)

Step IIa



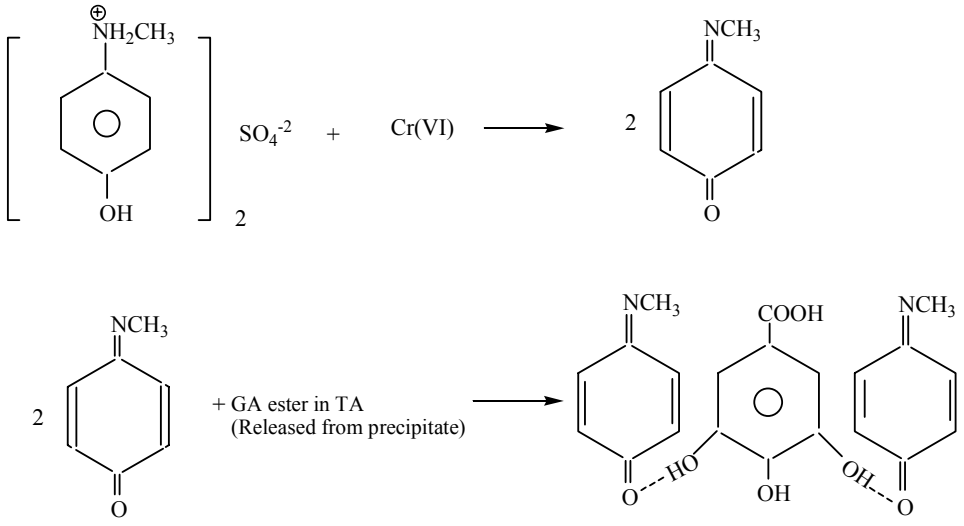
Step IIb



Method C

Step I: ZPD + TA → ZPD - TA + T.A
Adduct Unreacted
(Precipitate)

Step II



RESULTS AND DISCUSSION

The optimum conditions for the colour development of methods **A**, **B** and **C** were established by varying the parameters one at a time, keeping the others fixed and observing the effect produced on the absorbance of the coloured species.

The optical characteristics such as Beers law limits, molar absorptivity and Sandell's sensitivity for the methods (**A-C**) are given Table-1. The precision of the method to the drug was found by measuring the absorbance of 6 separate samples containing known amounts of drug and the results obtained are incorporated in Table-1. Regression analysis using the method of least squares was made to evaluate the slope (b), intercept (a) and correlation coefficient (r) and standard error of estimation (S_e) for each system and is presented in Table-1.

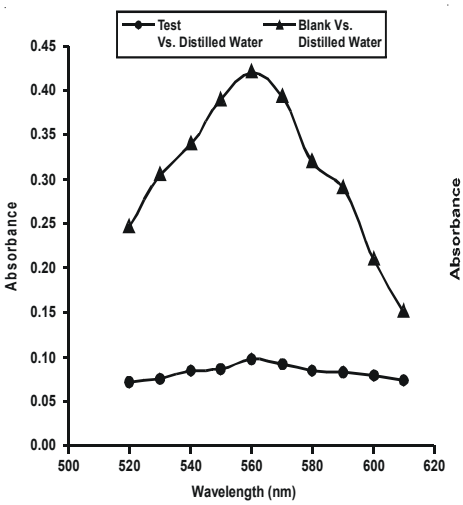
TABLE-1
OPTICAL CHARACTERISTICS, PRECISION AND ACCURACY OF THE PROPOSED METHODS OF ZIPARSIDONE

Parameters	Method **A**	Method **B**	Method **C**
λ_{max} (nm)	5.20	540	560
Beer's law limits (µg/mL)	4-24	0.4-2.4	8-48
Detection limit (µg/mL)	0.9330	0.0347	1.316
Molar absorptivity (L mol^{-1} cm^{-1})	5.94×10^3	1.722×10^5	2.899×10^3
Sandell's sensitivity (µg cm^{-2}/0.001 absorbance unit)	0.1838	2.231×10^{-2}	0.2937
Optimum photometric range (µg/mL)	5-17.78	1.1-2.4	20-48
Regression equation (Y = a + bc)	0.0137		
Slope (b)		0.3768125	0.0130
Standard deviation on slope (S_b)	2.98×10^{-4}	3.123×10^{-3}	9.85×10^{-5}
Intercept (a)	9.99×10^{-4}	0.01875	6.99×10^{-3}
Standard deviation on intercept (S_a)	3.95×10^{-4}	4.143×10^{-3}	2.61×10^{-3}
Standard error on estimation (S_e)	3.77×10^{-3}	3.950×10^{-3}	2.49×10^{-3}
Correlation coefficient (r)	0.993	0.9998	0.9996
Relative standard deviation (%)*	1.807	0.6271	1.542
0.05 level	2.09	0.7211	1.773
0.01 level	3.25	1.130	2.780
% Error in bulk samples**	0.102	0.166	0.282

The accuracy of the methods was ascertained by comparing the results by proposed and reference methods (UV) statitistically by the t- and F-tests (Table-2). The comparison shows that there is no significant difference between the results of studied methods and those of the reference ones. The similarity of the results is obvious evidence that during the application of these methods, the excipients are usually present in pharmaceutical formulations do not interfere in the assay of proposed methods. As an additional check of accuracy of the proposed methods, recovery experiments were carried out. The recovery of the added amounts of standard drug were studied at 3 different levels. Each level was repeated for 6 times. From the amount of drug found, the % recovery was calculated in the usual way.

TABLE-2
ASSAY OF ZIPARSIDONE HYDROCHLORIDE IN PHARMACEUTICAL FORMULATIONS

Formulations	Amount (mg)	Percentage recovery by proposed methods			Method **A**	Method **B**
		Method **A**	Method **B**	Reference method		
Tablet I	20	19.79±0.70 F=1.338 t=0.75	19.62±0.47 F=2.546 t=0.962	19.96±0.75	99.83±0.99	99.62±0.76
Tablet II	20	19.63±0.62 F=3.808 t=0.7	19.54±0.59 F=2.224 t=1.01	19.97±0.88	99.31±0.93	99.66±0.55
Tablet III	20	19.56±0.39 F=1.846 t=1.5	19.81±0.41 F=2.286 t=1.161	19.92±0.62	99.90±0.32	99.63±0.98
Tablet IV	20	19.65±0.43 F=2.215 t=0.88	19.73±0.48 F=3.008 t=0.67	19.97±0.76	99.54±0.60	99.68±0.98



Absorption spectrum of ZPD (TA/PMAP-Cr(VI)

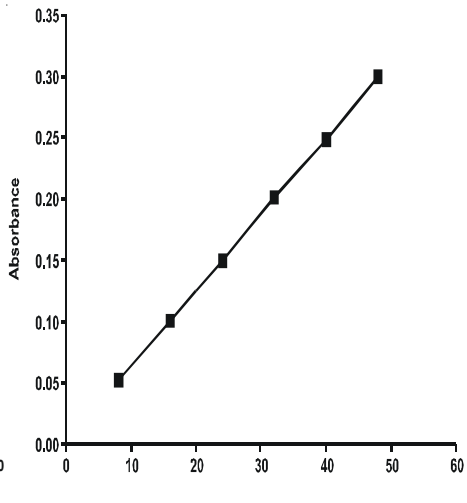


Fig. 3. Beer's law plot of ZPD-(TA/PMAP-Cr(VI)

The higher λ_{max} values of all the proposed methods have a decisive advantage since the interference from the associated ingredients should be generally less at higher wavelengths than at lower wavelengths. Thus the proposed visible spectrophotometric methods are simple and sensitive with reasonable precision, accuracy and constitute better alternatives to the existing ones to the routine determination of ZPD in bulk forms and pharmaceutical formulations.

Conclusion

The proposed methods exploit the various functional groups in ziparsidone hydrochloride (ZPD) molecule. The decreasing order of sensitivity ($\in_{max}$) among the proposed methods are (method **B** > method **A** > method **C**), respectively. The concomitants which do not contain the functional groups chosen in the present investigation do not interfere in the colour development by proposed methods. Thus the proposed methods are simple, sensitive and selective with reasonable precision and accuracy and constitute better alternatives to the reported ones in the assay of ZPD in bulk form and pharmaceutical formulations.

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