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# New Spectrophotometric Techniques for the Quantification of Zotepine – An Antipsychotic Drug

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## ABSTRACT

Zotepine is a second generation antipsychotic drug. It is used in the treatment of schizophrenia. Four novel, simple, precise and accurate spectrophotometric methods were developed for the determination of Zotepine in pharmaceutical dosage forms. The absorption maxima was found to be at 261 nm in hydrochloric acid (method A) and shows linearity over the concentration range of 0.1-50 µg/ml with regression equation 0.0621x + 0.00187 ($r^2$ = 0.999). Zotepine shows $\lambda_{max}$ at 261nm in sodium acetate buffer (pH 4.0) (method B) and obeys Beer Lambert's law over the concentration range 0.1-50 µg/ml with regression equation 0.061x + 0.012 ($r^2$= 0.999). First derivative spectrophotometric methods were also developed in hydrochloric acid and sodium acetate buffer (C and D) for the determination of Zotepine in which linearity was observed over a concentration range 0.1-50 µg/ml with regression equations 0.0038x + 0.0006 and 0.0038x + 0.0008 respectively. The proposed spectrophotometric methods were validated as per ICH guidelines and can be applied for the determination of Zotepine in pharmaceutical formulations.

**Key Words:** Zotepine, Spectrophotometry, Derivative spectroscopy, Validation.

## 1. INTRODUCTION

Zotepine (ZOT), chemically known as 2-[(8-chloro dibenzo (b,f) thiepin-10-yl)oxy]-N,N-dimethyl ethanamine is a second generation antipsychotic drug, a substituted dibenzothiepine tricyclic molecule, with effects on dopamine, serotonin and noradrenaline receptors(Green, 2009). Zotepine (Figure 1) is highly effective in acute exacerbation of schizophrenia. It has fewer adverse effects than conventional antipsychotics (Ulrich, 1996).

Literature survey revealed that Zotepine was determined by Gas liquid chromatographic method (Ulrich, 1996), LC-MS (Kumar, 2014), HPLC (Devi, 2012; Shruthi, 2014) and UV-Visible spectroscopy (Mrudula, 2013). In the present study the authors have proposed four simple validated spectrophotometric methods for the determination of Zotepine in pharmaceutical dosage forms.

## 2. MATERIALS AND METHODS

**2.1. Instrumentation:** A double beam UV-VIS spectrophotometer (UV-1800, Shimadzu, Japan) connected to computer loaded with spectra manager software UV Probe was employed with spectral bandwidth of 1nm and wavelength accuracy of ± 0.3 nm with a pair of 10 mm matched quartz cells. All weights were taken on electronic balance (Shimadzu).

**2.2. Chemicals and reagents:** Analytical grade methanol (Merck), glacial acetic acid (Merck), sodium hydroxide (Merck), hydrochloric acid (Merck) were used. Zotepine was obtained as gift sample from Symed Labs Limited (India) was used.

**2.3. Preparation of sodium acetate buffer (pH 4.0):** 2.86 ml of glacial acetic acid and 1.0 ml of 50% w/v solution of Sodium hydroxide was added in a 100 ml volumetric flask and made up the volume with double distilled water.

**2.4. Preparation of stock solution:** The standard solution of Zotepine was prepared by dissolving accurately about 25 mg of the Zotepine with methanol in a 25 ml volumetric flask.

The stock solution was further diluted with hydrochloric acid and sodium acetate buffer for method A (0.1-50 µg/ml) and method B (0.1-50 µg/ml) respectively as per the requirement.

**2.5. Procedure for preparation of calibration curve:** The drug solutions were scanned (200-400 nm) against reagent blank (hydrochloric acid for method A and sodium acetate buffer pH 4.0 for method B) and the absorption spectra were recorded. The absorption maximum ($\lambda_{max}$) was observed at 261 nm for method A and B. The absorption spectra so obtained were converted in to first derivative spectra by the inbuilt software of the instrument and the resulting spectrum shows both maxima and minima and therefore the magnitude of the amplitude was recorded against concentration for method C and D. Calibration curves were constructed by taking the concentration of the drug solutions on the x-axis and the corresponding absorbance values on the y-axis.

**2.6. Assay procedure for the marketed formulations (Tablets):** Zotepine is available with brand name Sirilept

(Labelled claim: 25 mg and 50mg of the drug per tablet) (Sun Pharmaceutical Industries Ltd., India) and were procured from the local pharmacy store. Twenty tablets were collected from each brand and ZOT equivalent to 25 mg was weighed and extracted with methanol, sonicated and make up to volume with methanol in two different 25 ml volumetric flasks (1 mg/mL) separately and filtered. The dilutions were made from this stock as per the requirement for method A, B, C and D and the percentage recovery was calculated.

**2.7. Precision and Accuracy:** The precision and accuracy studies were performed as per the ICH guidelines.The absorbance of six replicates (20 µg/mL) for Method A and B as well as the derivative absorbance of six replicates C and D were noted and the % RSD was calculated

Accuracy was evaluated as per the ICH guidelines by the percent recovery studies by the addition of 80%, 100%, and 120% of pure sample solution to the pre-analysed formulation solution. For the present study 5 µg/ml of ZOT solution extracted from the formulation was taken and 80%, 100%, and 120% of pure drug solution (i.e. 4, 5 and 6 µg/mL) were added and the % RSD was calculated.

## 3. RESULTS AND DISCUSSION

New spectrophotometric methods were developed for the determination of Zotepine in pharmaceutical preparations. Zotepine has shown absorption maxima ($\lambda_{max}$) at 261 nm in hydrochloric acid (Method A) and sodium acetate buffer pH 9.0 (Method B) and the corresponding absorption spectra were shown in Figure 2 and 3.

In method C, Zotepine has shown zero crossing points at 246.77 and 258.64 nm, with maxima at 253.58 nm and minima at 269.69 nm in Figure 4 and therefore the amplitude has been taken against the concentration for the construction of the calibration curve. Similarly in method D, Zotepine has shown zero crossing point at 246.77, 259.34, 283.87 and 294.21nm with maxima at 253.75 nm and minima at 269.46 nm in Figure 5 and therefore the amplitude has been taken against the concentration for the construction of the calibration curve.

Beer's law was obeyed in the concentration range of 0.1-50 µg/ml for the methods A, B, C and D. The linear regression equations were found to be y = 0.061x + 0.0254, y = 0.061x + 0.0166, y = 0.0038 + 0.0006 and y = 0.0038 + 0.0008 for method A, B, C and D respectively (Figure 6) with correlation coefficient 0.9997, 0.9998, 0.9996 and 0.9996 respectively (Table 1).

The % RSD values in precision studies were found to be 0.145, 0.487, 0.421 and 0.365 for method A, B, C and D respectively (RSD <2%) indicating that the method is more precise. The % RSD values in accuracy studies were found to be 0.189, 0.216, 0.342 and 0.415 for method A, B, C and D respectively (RSD <2%) indicating that the method is more accurate.

The percentage recovery (Table 2) was found to be in the range of 98.72-98.83, 98.77-98.90, 98.51-98.79 and 98.69-98.81 for method A, B, C and D respectively (RSD <1.0 %) indicating that the proposed methods can be applied for the determination of pharmaceutical formulations successfully.

**Table. 1. Optical characteristics of Zotepine**

| Parameters | Method | | | |
|---|---|---|---|---|
| | A | B | C | D |
| Beer-Lambert's limits (µg /ml) | 0.1-50 | 0.1-50 | 0.1-50 | 0.1-50 |
| $\lambda_{max}$ /Amplitude range (nm) | 261 | 261 | 253.58 - 269.69 | 253.75 – 269.46 |
| Molar extinction coefficient (litre/mol.cm) | $2.120584\times10^4$ | $2.16040\times10^4$ | - | - |
| Sandell's sensitivity (µg/cm$^2$/0.001absorbance unit) | 0.01564 | 0.01536 | - | - |
| Slope | 0.061 | 0.061 | 0.0038 | 0.0038 |
| Intercept | 0.0254 | 0.0166 | 0.0006 | 0.0008 |
| Correlation coefficient | 0.9997 | 0.9998 | 0.9996 | 0.9996 |

**Table. 2. Assay of marketed formulations of Zotepine (Tablets)**

| Brand | Labelled Amount (mg) | *Amount obtained (mg) | | | | % Recovery* | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Method | | | | Method | | | |
| | | A | B | C | D | A | B | C | D |
| Sirilept | 25.0 | 24.707 | 24.725 | 24.698 | 24.702 | 98.83 | 98.90 | 98.79 | 98.81 |
| | 50.0 | 49.459 | 49.385 | 49.255 | 49.347 | 98.72 | 98.77 | 98.51 | 98.69 |

*Mean of three determinations

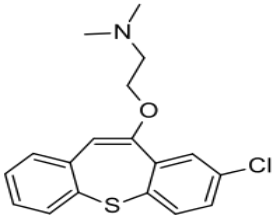



**Figure. 1. Chemical structure of Zotepine (ZOT)**

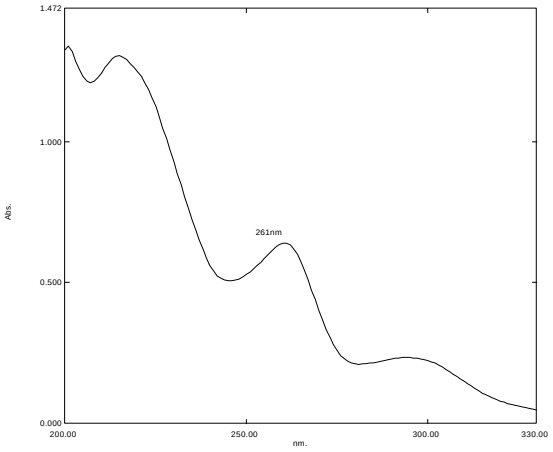



**Figure. 2. Absorption spectrum of Zotepine (10 µg/mL)in Hydrochloric acid**

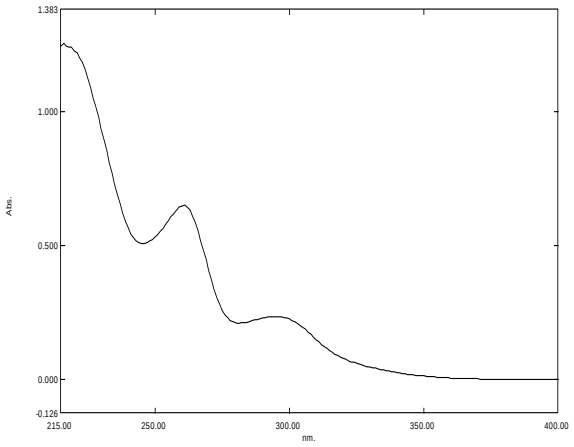



**Figure. 3. Absorption spectrum of Zotepine (10 µg/mL) in sodium acetate buffer**

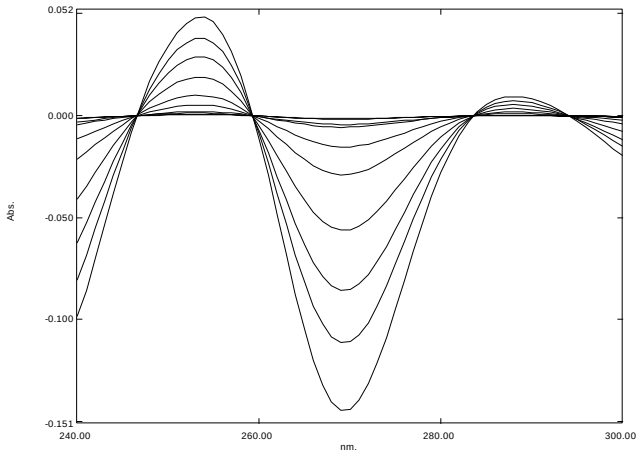



**Figure. 4. Overlay first derivative spectra ($D_1$) of Zotepine in hydrochloric acid**

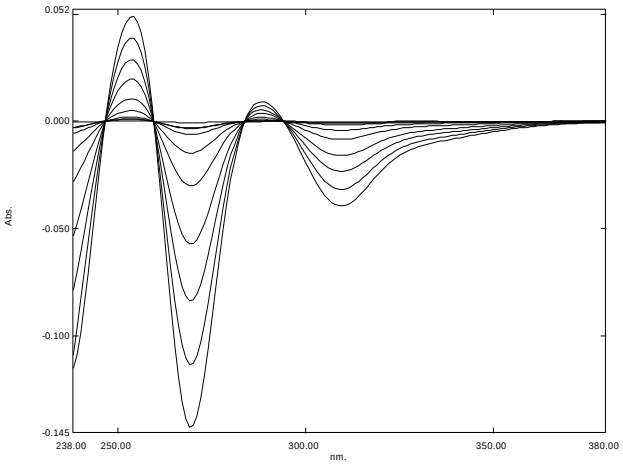
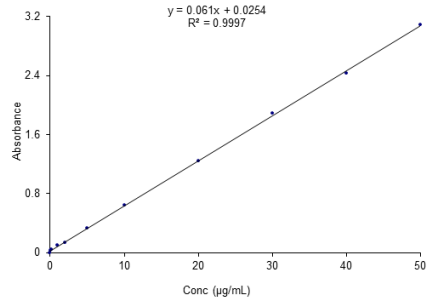
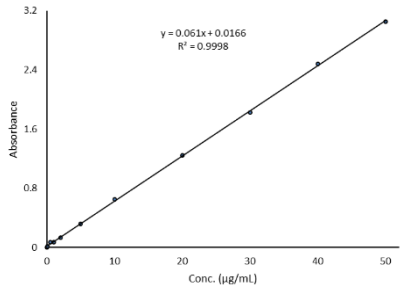



**Figure. 5. Overlay first derivative spectra ($D_1$) of Zotepine in sodium acetate buffer (pH 4.0)**




[A]

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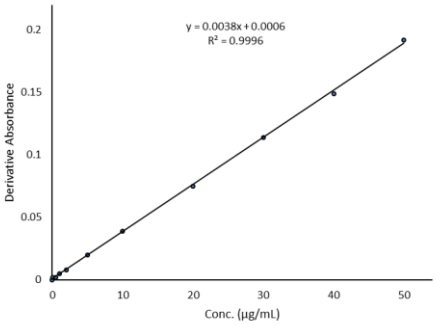


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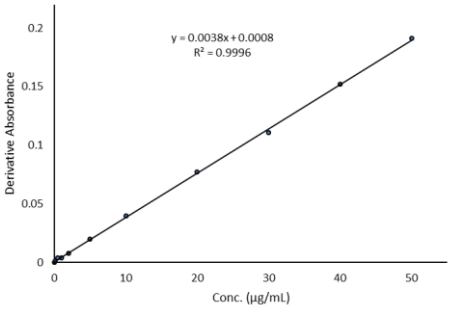


[D]

**Figure.6. Calibration curves of Zotepine in method A, B, C and D**

## 4. CONCLUSION

The present methods can be employed for the determination of Zotepine in pharmaceutical formulations successfully and there is no interference of excipients during the study.

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