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ORIGINAL PAPER

Stability-Indicating Spectrofluorimetric Method for the Assay of Ziprasidone in Capsules

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Abstract A simple, rapid and highly sensitive spectrofluorimetric method was developed for determination of ziprasidone hydrochloride (ZPS) in capsules. The method is based on measuring the native fluorescence of ZPS in acetate buffer of pH 4.5 at 398 nm after excitation at 315 nm. The fluorescence-concentration plot was rectilinear over the range of 0.05–0.80 μg mL^{-1} with a lower detection limit (LOD) of 6.0 ng mL^{-1} and quantification limit (LOQ) of 20.0 ng mL^{-1}. The method was fully validated and successfully applied to the determination of ZPS in its capsules with average percentage recovery of 99.7±1.4. The method was extended to stability study of ZPS. The drug was exposed to acidic, alkaline, oxidative and photolytic degradation according to ICH guidelines. Moreover, the method was utilized to investigate the kinetics of the alkaline, acidic and oxidative degradation of the drug. A proposal for the degradation pathways was postulated.

Keywords Ziprasidone · Spectrofluorimetry · Capsules · Stability-indicating

Introduction

Ziprasidone, (ZPS, Fig. 1), 5-{2-[4-(1,2-Benzisothiazol-3-yl)-1- piperazinyl]ethyl}-6-chloro-2-indolinone, is an indole-like heterocyclic antipsychotic agent. Ziprasidone is an atypical antipsychotic drug reported to have affinity for adrenergic (α_1), histamine (H_1), and serotonin ($5\text{-}HT_2$) receptors as well as dopamine (D_2) receptors. It is used for the treatment of schizophrenia and in acute manic or mixed episodes associated with bipolar disorder [1].

Literature survey revealed that several analytical methods were reported for the determination of ZPS in biological matrices, including; liquid chromatography-tandem mass spectrometry [2–5], liquid chromatography/UV detection [6], liquid chromatography/fluorescence detection [7]. Meanwhile, some analytical methods have been reported for the determination of ZPS in raw material and pharmaceutical formulations including; TLC densitometry [8], HPLC/UV detection [8–10], capillary zone electrophoresis [11] and spectrophotometric methods [12, 13].

To the best of our knowledge, up till now nothing has been published concerning the specrofluorimetric determination of ZPS. Therefore, the current study was aimed to develop and validate a simple, rapid and sensitive spectrofluorimetric methodology for the determination of ZPS utilizing its native fluorescence. The proposed method was fully validated according to ICH guidelines, and successfully applied for the determination of the drug in its capsules.

The parent drug stability guidelines issued by the International Conference on Harmonization (ICH) [14] requires that, analytical test procedure should indicate stability. Therefore, the present study was extended to establish the inherent stability of ZPS under different stress conditions such as, alkaline, acidic, oxidative and photolytic conditions.

Experimental

Apparatus

– The fluorescence spectra and measurements were recorded using a Perkin-Elmer model LS 45 lumines-

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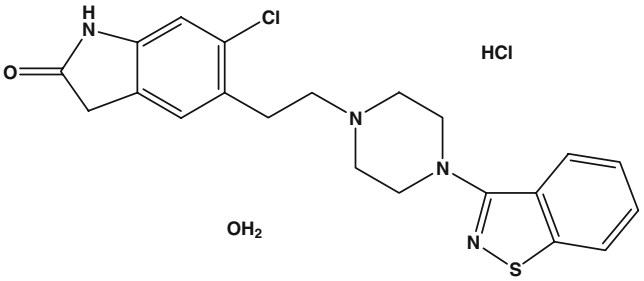


Fig. 1 Chemical structure of ziprasidone hydrochloride monohydrate (ZPS)

cence Spectrometer (UK), equipped with a 150 W Xenon arc lamp, grating excitation and emission monochromators and a PerkinElmer recorder. Slit widths for both monochromators were set at 10 nm. A 1-cm quartz cell was used.
- Hanna pH-Meter (Romania) was used for pH adjustments.
- CAMAG UV-lamp (S/N 29000), dual wavelength (254/366), 2×8 W (Muttenz, Switzerland) was used in the photo-stability study.

Materials and Reagents

All reagents used were of Analytical Reagent Grade, and distilled water was used through out the study:

- Ziprasidone hydrochloride monohydrate pure sample was obtained from Pfizer Co. through Drug Control Center, Riyadh, Saudi Arabia, and was used as received. Its purity was found to be 99.47% according to the comparison method [13].
- Zeldox® capsules, batch # 910024732, labeled to contain 60 mg ziprasidone hydrochloride monohydrate/capsule, product of Heinrich Mack Nachf, Germany, a subsidiary of Pfizer Inc., was purchased from local pharmacy.
- β-cyclodextrin (β-CD) and hydroxy propyl-β-cyclodextrin (HP-β-CD) (Merck, Germany), 0.5% aqueous solutions were prepared in hot distilled water.
- Tween-80 (Adwic Co., Egypt), 0.5% aqueous solution was prepared.
- Sodium dodecyl sulfate (SDS, 95%) and cetyltrimethyl ammonium bromide (CTAB, 99%) (Winlab, UK), 0.5% aqueous solutions were prepared.
- Sodium acetate trihydrate (0.2 M solution), sodium hydroxide (0.2 and 0.5 M solutions), boric acid (0.2 M solution) (BDH, UK).
- Hydrochloric acid (2 M solution), hydrogen peroxide (6% w/v solution), dimethyl formamide (DMF) (BDH, UK).
- Methanol (Sigma, Germany).
- Dimethyl sulfoxide (DMSO) and n-propanol (Riedel-deHäen, Germany).
- Acetate buffer solutions (0.2 M), covering the pH range of 3.6–5.6, were prepared by mixing appropriate volumes of 0.2 M sodium acetate trihydrate and 0.2 M acetic acid and adjusting the pH using a pH-Meter.
- Borate buffer solutions (0.2 M), covering the pH range of 6.5–9.5, were prepared by mixing appropriate volumes of 0.2 M boric acid and 0.2 M NaOH and adjusting the pH using a pH-Meter.

Stock and Standard Solutions

A stock solution containing100 μg mL^{-1} of ZPS was prepared in methanol. This solution was further diluted with the same solvent to obtain a standard solution containing 5 μg mL^{-1} of ZPS. The solutions were stable for 2 weeks when kept in the refrigerator and protected from light.

General Procedures

- Construction of calibration graph

  Accurately measured volumes of the standard solution of ZPS were transferred into a series of 10 mL volumetric flasks to give final concentrations of 0.05–0.80 μg mL^{-1}. 2 mL of 0.2 M acetate buffer solution of pH 4.5 were added; the solutions were completed to the volume with distilled water and mixed well. The fluorescence intensities were measured at 398 nm after excitation at 315 nm. The relative fluorescence intensities were plotted versus the final concentration of the drug (μg mL^{-1}) to get the calibration graph; alternatively, the corresponding regression equation was derived.
- Procedure for capsules

  The contents of ten capsules were emptied, mixed well and pulverized. An accurately weighed quantity of the powder equivalent to 10.0 mg of ZPS was transferred into 100 mL volumetric flask and sonicated with 80 mL of methanol for 30 min. The volume was completed with methanol and the solution was filtered. The solution was diluted with methanol to obtain a standard solution containing 5 μg mL^{-1} of ZPS. The procedure described under "*Construction of calibration graph*" was followed. The nominal content of the capsules was calculated using the calibration graph or the corresponding regression equation.
- Procedures for stability studies

• Alkaline and acidic degradation

  Aliquots of ZPS stock solution (containing 100.0 μg) were transferred into two series of small conical flasks; 5 mL of 0.5 M NaOH or 2.0 M HCl solutions were added. The solutions were heated in a boiling water bath for different time intervals (15–75 and 5–25 min

for alkaline and acidic degradation, respectively). At the specified time, the contents of each flask were cooled; neutralized to pH 7 with either 0.5 M HCl or 2.0 M NaOH, respectively. The solutions were then quantitatively transferred into 25 mL volumetric flasks and completed to volume with methanol. 1.0 mL of the resulting solutions was then transferred into 10 mL volumetric flasks and the procedure described under "*Construction of calibration graph*" was performed.

- Oxidative degradation

  Aliquots of ZPS stock solution (containing 100.0 μg) were transferred into a series of small conical flasks; 5 mL of 6% (w/v) H_2O_2 solution were added and the solutions were heated in a thermostatically controlled water bath at different temperature settings (50–80 °C) for different time intervals (10–50 min). At the specified time, the contents of each flask were cooled; the solutions were then quantitatively transferred into 25 mL volumetric flasks and completed to volume with methanol. 1.0 mL of the resulting solutions was transferred into 10 mL volumetric flasks and completed as under "*Construction of calibration graph*"

- Photolytic degradation

  Aliquots of ZPS stock solution (containing 100.0 μg) were transferred into a series of 25 mL volumetric flasks and diluted to the volume with either methanol, water, or methanol/water mixture (50:50, v/v). The solutions were exposed to UV-lamp at a wavelength of 254 nm at a distance of 15 cm placed in a wooden cabinet for 24 h. At the specified time, the flasks were removed from the UV-lamp cabinet. 1.0 mL of the solutions was then transferred into 10 mL volumetric flasks and the procedure described under "*Construction of calibration graph*" was followed.

Results and Discussion

The ultraviolet spectrum of aqueous buffered solution of ZPS at pH 4.5 exhibits two absorption maxima at 237 and 315 nm, with a specific absorbance [$A_{1\%,\ 1cm}$] of 1,000 and 144, respectively. As a consequence, poor sensitivity will be achieved by conventional spectrophotometric measurements. This problem is highly aggravated when it is needed to determine the drug especially in pharmaceutical preparations. This fact led us to investigate the native fluorescence behavior of ZPS in an attempt to develop a sensitive, simple and reliable method for its determination. Different experimental parameters affecting the fluorescence intensity of ZPS were carefully studied and optimized. Such factors were changed individually, where others kept constant. Furthermore, the developed method was applied to establish the inherent stability of ZPS under different stress conditions according to ICH guidelines [14].

– Fluorescence spectra and characteristics of ZPS

  Ziprasidone was found to exhibit an intense native fluorescence in aqueous acetate buffer solution of pH 4.5 at 398 nm after excitation at 315 nm (Fig. 2). It is clear that, ZPS exhibits two excitation wavelengths of 237 and 315 nm. This is justified in theory by the light absorption promoting electron from the ground electronic state to two excited states [15]. A wavelength of 315 nm was selected as the optimum excitation wavelength since it gave the sharpest emission spectrum with best reproducibility and linearity. Fluorescence scan analysis showed best combination at 315 and 398 nm as excitation and emission wavelengths, respectively.

– Study of Experimental Parameters

- Effect of pH

  The influence of pH on the native fluorescence intensity of ZPS was studied using 0.01 M HCl (pH=2.0) and different types of buffer solutions covering the pH range of 3.6–9.5. It was found that, the maximum and constant relative fluorescence intensity (RFI) was achieved over the pH range of 3.6–5.6, so that; pH 4.5 was chosen as the optimum pH value. Increasing the pH value more than pH 5.6 caused gradual decrease of the RFI of ZPS (Fig. 3).

- Effect of different organized media

  The influence of different surfactants and macromolecules on the native fluorescence intensity of ZPS was studied; hopefully, a significant increase in the fluorescence intensity could be achieved. Different surfactants such as anionic surfactant (SDS), cationic surfactant (CTAB), non-ionic surfactant (tween-80), and different macromolecules such as β-CD, HP-β-CD and methyl cellulose (1 mL of 0.5% aqueous solution of each) were investigated. It was found that, methyl cellulose did not affect the fluorescence intensity of ZPS. On the other hand, β-CD, HP-β-CD, CTAB, SDS and tween-80 caused a significant decrease in the fluorescence intensity of ZPS. Therefore, no surfactant was used throughout this study.

- Effect of diluting solvent

  Dilution with different solvents such as water, methanol, acetonitrile, n-propanol, DMF and DMSO were studied. Water was the best solvent for dilution since it gave the highest RFI and the lowest blank reading with reproducible results. A distinct and sharp decrease of the fluorescence intensity was observed upon using methanol, acetonitrile and n-propanol for dilution; this may be attributed to change in the medium polarity that may result in

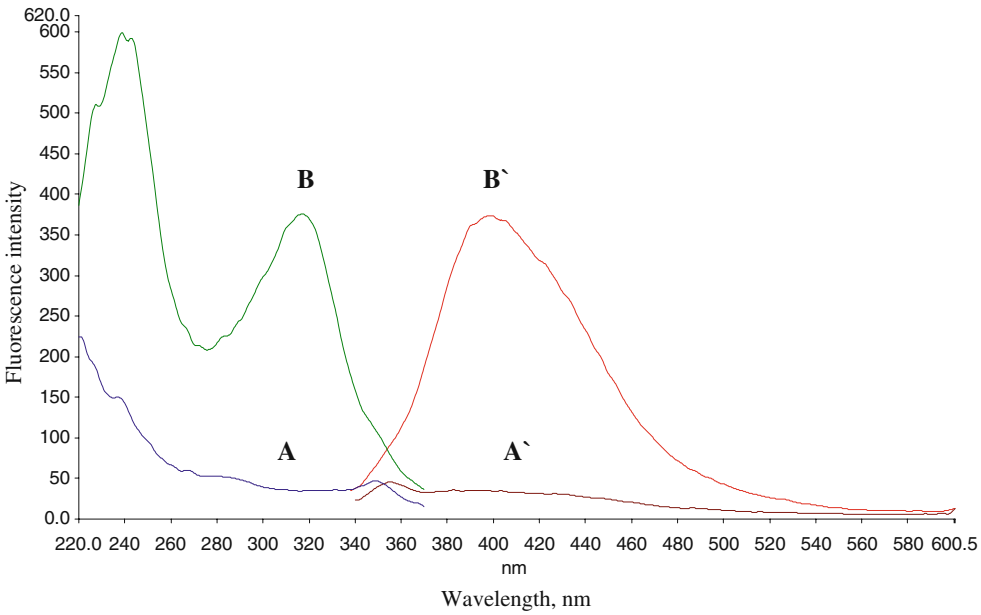


Fig. 2 Flurescence spectra of: (A, A′): Acetate buffer of pH 4.5. (B, B′): ZPS (0.4 μg mL^{-1}) in acetate buffer of pH 4.5. Where: (A, B) are the excitation spectra. (A′, B′) are the emission spectra

some sort of physical interaction between these solvents and the excited singlet state of the drug molecules. On the other hand, DMF and DMSO greatly quenched the fluorescence of ZPS (Fig. 4), since they initiated intersystem crossing process (similar to heavy atom effect) [16].

- Effect of time

  The effect of time on the RFI of ZPS was also studied. It was found that the fluorescence intensity was immediately developed and remained stable for more than 2 hours.

- Effect of temperature

  Another factor that affects the fluorescence intensity is temperature. The effect of temperature was studied in the range of 40–100 °C using a thermostatically controlled water bath. It was found that increasing the temperature resulted in a gradual decrease in the RFI. This effect can be attributed to higher internal conversion as the temperature increases, facilitating non-radiative deactivation of excited singlet state and increase of the loss of energy *via* collision with solvent molecules [17]. Therefore, the study was carried out at room temperature (25 °C).

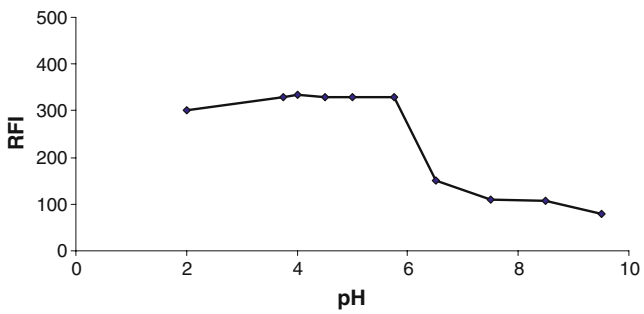


Fig. 3 Effect of pH on RFI of ZPS (0.4 μg mL^{-1})

Validation of the Method

The validity of the proposed method was tested using the following criterion: linearity, sensitivity, limit of detection, limit of quantitation, specificity, accuracy, precision and robustness according to ICH recommendations [18].

- Linearity and range

  Assessment of linearity of the assay method was performed by analyzing seven sets (standard calibration curve). Adopting the previous procedure, a linear regression equation was obtained. The regression plot showed a linear dependence of RFI on drug concentration over the range of 0.05–0.80 μg mL^{-1}. Statistical evaluation of the regression data for ZPS regarding

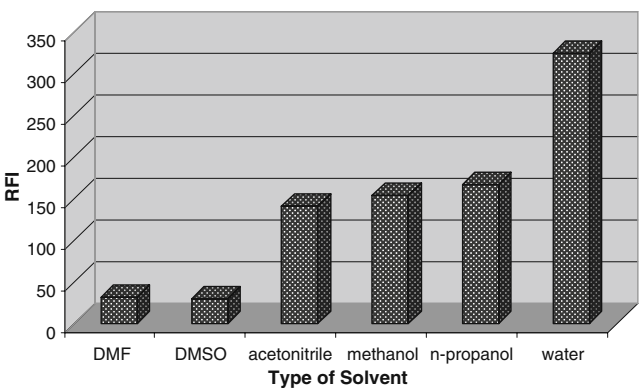


Fig. 4 Effect of the type of diluting solvent on RFI of ZPS (0.4 μg mL^{-1}) in aqueous acetate buffer of pH 4.5

Table 1 Performance data for the proposed spectrofluorimetric method for determination of ZPS

Parameter	Results
Concentration range (μg mL^{-1})	0.05–0.80
Limit of detection (LOD) (ng mL^{-1})	6.0
Limit of quantification (LOQ) (ng mL^{-1})	20.0
Correlation coefficient(r)	0.9999
Slope	743.0
Intercept	20.2
$S_{y/x}$	3.1
S_a	1.5
S_b	4.7
% RSD	1.4
% Error	0.5

Where:

$S_{y/x}$ Standard deviation of the residuals

S_b Standard deviation of the slope

% Error=% RSD/√n

S_a Standard deviation of the intercept

standard deviation of the residual ($S_{y/x}$), standard deviation of the intercept (S_a) and standard deviation of the slope (S_b) is given in Table 1 [19]. The small values of the figures point out to low scattering of the points around the calibration curve, thus, indicating the high accuracy and high precision of the method, respectively.

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

The limit of quantification (LOQ) and limit of detection (LOD) were determined according to ICH Q2 (R1) recommendations [18]. The results are summarized in Table 1.

LOQ and LOD were calculated according to the following equations:

$$LOQ = 10S_a/b$$

$$LOD = 3.3S_a/b$$

Where, S_a is the standard deviation of the intercept of regression line and b is the slope of the regression line.

- Sensitivity:

The sensitivity of the assay is defined as the change in response with the change in the concentration of the drug. The proposed method is highly sensitive since a high change in response is achieved with the small change in concentration as indicated by the high value of the slope (Table 1).

- Accuracy:

The accuracy of the proposed method is defined as the similarity of the results obtained by this method to

Table 2 Assay of ZPS in pure sample and commercial capsules using the proposed and comparison methods

Parameter	Proposed method			Comparison method [13]	
	Conc. taken (μg mL^{-1})	Conc. found (μg mL^{-1})	%Recovery	Conc. taken (μg mL^{-1})	% Recovery
Pure form	0.05	0.051	102.00	5.0	98.60
	0.10	0.099	99.00	8.0	100.40
	0.20	0.199	99.50	10.0	99.40
	0.30	0.306	102.00		
	0.40	0.396	99.00		
	0.60	0.597	99.50		
	0.80	0.804	100.50		
$\bar{x} \pm$ S.D.			100.1±1.4		99.5±0.9
t			1.438(2.365)*		
F			5.563(19.3)*		
Zeldox® capsules (60 mg ZPS/Cap.)	0.10	0.101	101.0	5.0	98.7
	0.30	0.295	98.4	8.0	99.4
	0.60	0.589	98.1	10.0	101.2
$\bar{x} \pm$ S.D.			99.7±1.4		99.8±1.3
t			1.619(19.0)*		
F			2.582(2.776)*		

Each result is the average of three separate determinations

*Values between brackets are the tabulated *t* and *F* values, at p=0.05[19]

Table 3 Precision data for the proposed method of determination of ZPS in pure form

Conc. (μg mL^{-1})	% Recovery[a]	% RSD	% Error
Intraday precision			
0.10	98.60±1.4	1.4	0.8
0.30	97.71±1.4	1.4	0.8
0.60	99.96±1.0	1.0	0.6
Interday precision			
0.10	100.2±1.2	1.2	0.7
0.30	101.2±0.8	0.8	0.5
0.60	98.6±0.9	0.9	0.5

[a] Each result is the average of three separate determinations

the true values. To test the validity of the method it was applied to the determination of pure samples of ZPS over the range of 0.05–0.80 μg mL^{-1}. The results obtained were in good agreement with those obtained using the comparison spectrophotometric method [13]. Using the student *t*-test and the variance ratio *F*-test revealed no significant difference between the performance of the two methods regarding the accuracy and precision, respectively (Table 2).

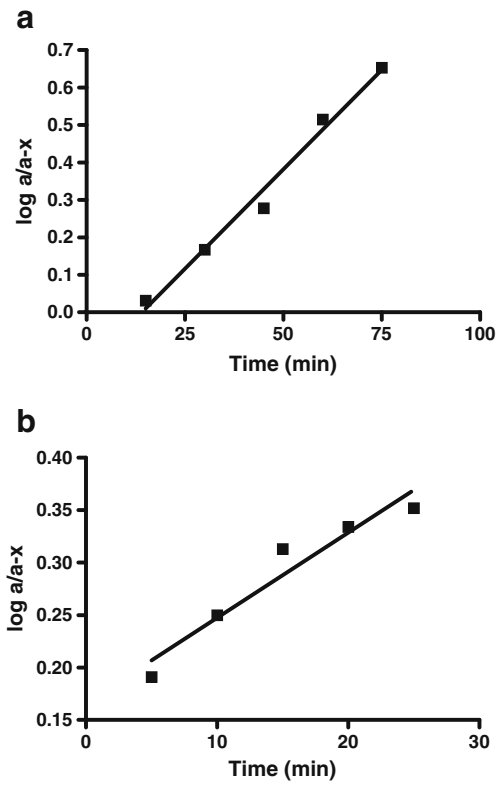


Fig. 5 **a** Effect of boiling time with NaOH (0.5 M) on ZPS (0.4 μg mL^{-1}). **b** Effect of boiling time with HCl (2.0 M) on ZPS (0.4 μg mL^{-1})

Table 4 Results of the degradation study of ZPS under different stress conditions

Degradation condition	Reaction rate constant (K, min^{-1})	Half life time ($t_{1/2}$, min)
Alkaline degradation (0.5 M NaOH, 100 °C)	0.025	28
Acidic degradation (2.0 M HCl, 100 °C)	0.019	37
Oxidative degradation (6% H_2O_2, 80 °C)	0.035	20

- Precision:

  The intra-day precision was evaluated through replicate analysis of different concentrations of the drug in pure form within the specific working concentration range. Each sample was analyzed three successive times. The results are summarized in Table 3.

  Similarly, the inter-day precision was evaluated through replicate analysis of the three different concentrations on three successive days. The results obtained are abridged also in Table 3.

  The data presented in Table 3 indicate high accuracy and precision of the developed method. The high value of the average percentage recovery and the small value of% RSD indicate the high accuracy and precision, respectively.

- Robustness:

  The robustness of the proposed method was demonstrated by the constancy of RFI with the deliberated minor changes in the experimental parameters such as pH, 4.5±0.5, volume of buffer, 2.0±0.5 mL. These minor changes that may take place during the experimental operation did not greatly affect the fluorescence intensity of ZPS.

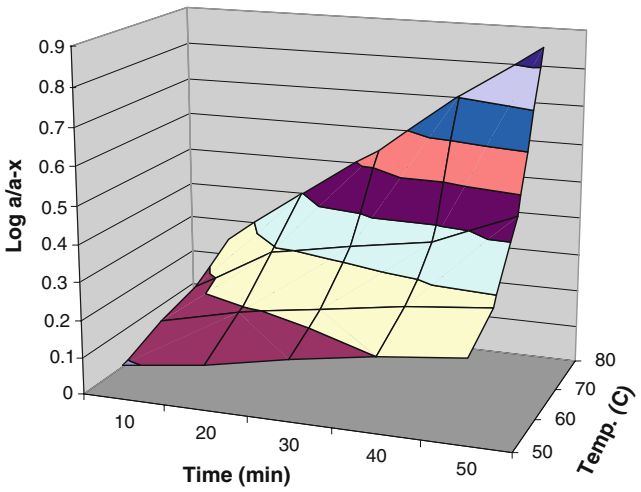


Fig. 6 Three-dimensional plot showing the effect of heating time with H_2O_2 solution (6% w/v) on ZPS (0.4 μg mL^{-1}) at different heating temperatures

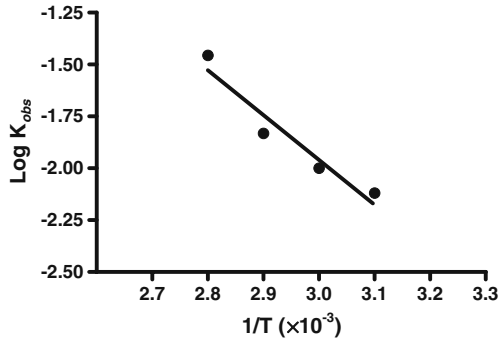


Fig. 7 Arrhenius plot for the oxidative degradation of ZPS in 6% (w/v) H_2O_2

- Specificity:

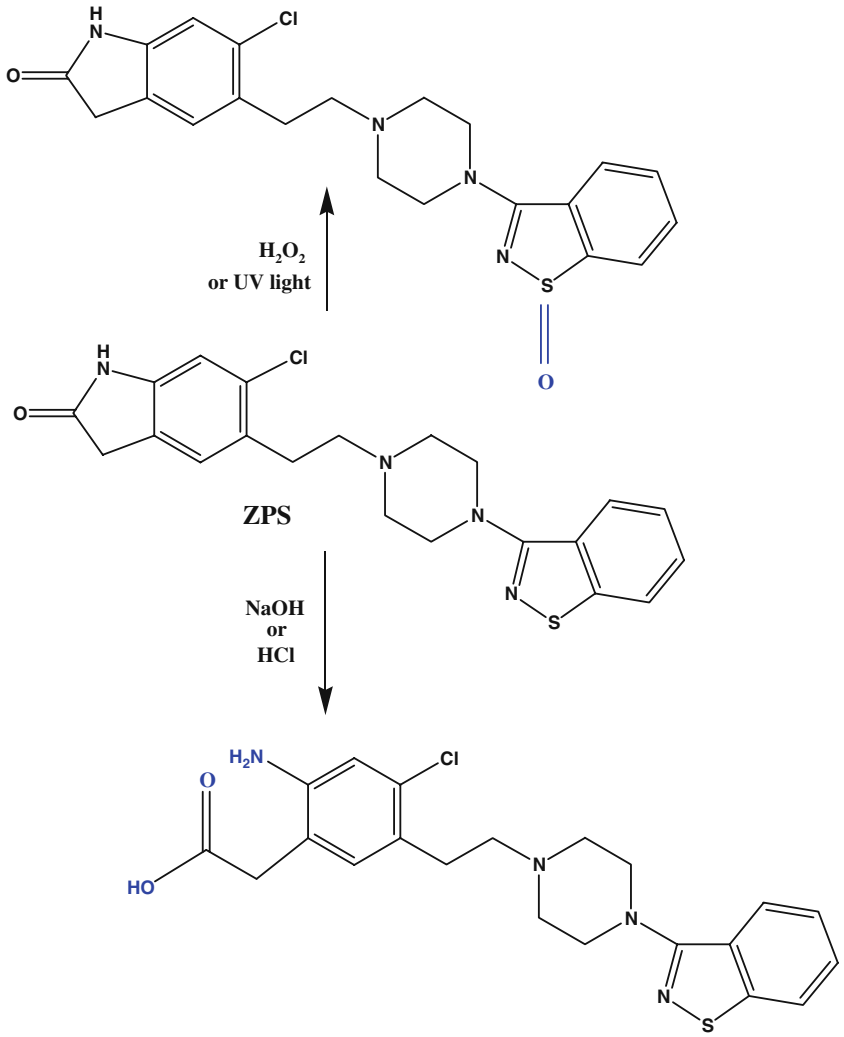
  The specificity of the proposed procedure was proven by its ability to determine ZPS in its capsules confirming that, there was no interference by common excipients and additives; such as lactose, pregelatinized starch and magnesium stearate. These matrix components did not interfere with the proposed method (Table 2). This was revealed by carrying out the same experiment using placebo capsule and omitting the drug.

Results of Stability Studies and Degradation Kinetics

The alkaline treatment of ZPS with 0.5 M NaOH was accompanied by a gradual decrease in the fluorescence intensity. The alkaline degradation of ZPS was found to be time dependent (Fig. 5a). Upon boiling with 0.5 M NaOH for 75 min, about 78% degradation of the original sample occurred. The apparent first order degradation rate constant and half-life time were calculated (Table 4).

Considerable degradation was also observed in ZPS sample under acidic stress condition. The acidic degradation of ZPS was found to be time dependent (Fig. 5b), after boiling with 2.0 M HCl solution for 40 min, about 56% of the original drug sample was degraded. The apparent first

Scheme 1 Proposal for the degradation pathways of ZPS



order rate constant and half-life time were also calculated (Table 4).

Degradation of ZPS under oxidative stress conditions was also studied. The oxidative degradation of ZPS was found to be temperature and time dependent. Figure 6 is a three dimensional plot showing the effect of different heating times (10–50 min) with H_2O_2 solution (6%, w/v) at different heating temperatures (50–80 °C). The apparent first order degradation rate constant and half-life times were also calculated (Table 4). By plotting log K_{obs} values versus 1/T, Arrhenius plot was obtained (Fig. 7). The activation energy, E_a, was calculated and was found to be 10.0 K. Cal.mol^{-1}. Arrhenius equation was derived and it was found to be:

$$\text{Log K} = 4.515 - (2.16/\text{T})$$

The effect of UV-light on the stability of ZPS was also studied by exposing ZPS solutions in different solvents (methanol, water, methanol/water mixture, 50/50, v/v) to the UV-light at 254 nm. It was found that a significant decrease in the RFI of ZPS was observed upon exposure of aqueous solution of the drug to UV-light for 24 h (31% degradation), on the other hand, mild degradation was observed in methanolic solution of ZPS (only 9% degradation of the original sample) when irradiated for the same period. This can be explained by the fact that, polar solvents tend to increase the degradation of drug molecules that produce degradates which are more polar than the original drug, and non-polar solvents enhance the degradation of polar compounds that produce less polar degradates [20]. This could be a possible explanation for the decreased stability of the drug solutions containing water, where, it is expected that, the photolytic degradation of ZPS proceeds through photo-oxidation of the sulfur atom yielding the corresponding sulphoxide derivative of ZPS which is more polar than the parent drug itself. This proposal is based on previous reports concerned with the photodegradation of organosulfur compounds, proving that the photodegradation of sulfur containing compounds proceeds *via* sulphoxide formation [21].

The main pathway of H_2O_2 degradation is proposed to proceed *via* oxidative degradation with the formation of the corresponding sulphoxide derivative.

Alkaline and acidic degradation of ZPS occurred significantly at boiling temperature, where, at lower temperatures the degradation is mild. The alkaline and acidic treatments of ZPS are expected to cause cleavage of the indole ring resulting in decrease of the native fluoresecence intensity of the drug.

TLC fractionation of the hydrolysates obtained following the exposure of ZPS to alkaline, acidic, oxidative and photolytic degradation, utilizing silica gel sheets 60 F_{254} (5 cm×10 cm with 0.2 mm thickness), run with solvent composed of chloroform: methanol: glacial acetic acid (75: 5: 4.5 mL, v/v); visualized under UV lamp at 254 nm [8], revealed that;

- Under oxidative and photolytic conditions, one spot was obtained in each case corresponding to the same degradation product with characteristic R_f value of 0.1. These results indicate that the degradation followed the same pathway under oxidative and photolytic conditions.
- Acidic and alkaline degradation of ZPS yield the same degradation product that's retained on the base line, indicating that the degradation pathways are the same under acidic and alkaline conditions.
- The R_f value of the intact ZPS drug substance is 0.75.
- The spot of the higher R_f value (0.1) is corresponding to the degradation product of less polarity (sulphoxide derivative), while the degradation product that remained on the base line is more polar due to the free amino and carboxylic groups resulted from cleavage of the indole ring.

A proposal for the possible degradation pathways of ZPS is presented in Scheme 1.

Applications of the Proposed Method to the Determination of ZPS in Capsules

The proposed method was successfully applied to the assay of ZPS in commercial capsules. The average percent recoveries of different concentrations were based on the average of three replicate determinations. The results shown in Table 2 are in good agreement with those obtained with the comparison spectrophotometric method [13].

Conclusion

The developed spectrofluorimetric method provided a reliable, reproducible and specific assay for ZPS in pharmaceutical preparations. The method is sensitive enough to detect as low as 6 ng mL^{-1} of ZPS. Based on problems encountered from post publications, the present study has served to develop a simple, satisfactory, rapid, and fully validated assay method of ZPS in pharmaceutical preparations.

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