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ORIGINAL RESEARCH

# Stability indicating reversed-phase high-performance liquid chromatographic and thin layer densitometric methods for the determination of ziprasidone in bulk powder and in pharmaceutical formulations

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ABSTRACT: Two sensitive and reproducible methods were developed and validated for the determination of ziprasidone (ZIP) in the presence of its degradation products in pure form and in pharmaceutical formulations. The first method was based on reversed-phase high-performance liquid chromatography (HPLC), on a Lichrosorb RP $C_{18}$ column using water:acetonitrile:phosphoric acid (76:24:0.5 v/v/v) as the mobile phase at a flow rate of 1.5 mL $min^{-1}$ at ambient temperature. Quantification was achieved with UV detection at 229 nm over a concentration range of 10–500 μg $mL^{-1}$ with mean percentage recovery of 99.71 ± 0.55. The method retained its accuracy in presence of up to 90% of ZIP degradation products. The second method was based on TLC separation of ZIP from its degradation products followed by densitometric measurement of the intact drug spot at 247 nm. The separation was carried out on aluminium sheet of silica gel 60 $F_{254}$ using choloroform:methanol:glacial acetic acid (75:5:4.5 v/v/v) as the mobile phase, over a concentration range of 1–10 μg per spot and mean percentage recovery of 99.26 ± 0.39. Both methods were applied successfully to laboratory prepared mixtures and pharmaceutical capsules. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: ziprasidone; antipsychotic drug; pharmaceutical capsules; bulk materials; purity evaluation; degradation products

## INTRODUCTION

Ziprasidone (ZIP, Fig. 1), 5-[2-[2-(1,2-benzisothiazol-3-yl-1lpiperazinyl] ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one; 5-(2-(4-(1,2-benzisothiazol-3-yl) piperazinyl) ethyl)-6-chlorooxindole is a typical antipsychotic drug used for the treatment of schizophrenia (Gunasekara *et al.*, 2000a,b). It was reported to have an affinity for serotonin (5HT 2) and dopamine (D2) receptors (Gunasekara *et al.*, 2000b; Clay and Cooper, 2002). Few methods have been reported for ZIP determination by mass spectroscopy (Janiszewski *et al.*, 1998), and HPLC (Janiszewski *et al.*, 1995; Pfeizer Inc., personal communication). None of the reported methods determined the drug in the presence of its degradation products, which may result from decomposition of ZIP under storage conditions or during the synthesis of the bulk materials. The parent drug stability guidelines issued by the International Conference on Harmonization (ICH) requires that analytical test procedure should indicate stability (ICH, 2003). HPLC and TLC techniques have been reported for the determination of many drugs in presence of their degradation products e.g. bronopol (Wang *et al.*, 2002), haloperidol (Trabelsi *et al.*, 2002), diloxanide furoate (Hasan *et al.*, 2002) and loratadine (El Ragehy *et al.*, 2002). Accordingly, the aim of the present study was to develop a validated stability-indicating chromatographic method for the purity evaluation and quantitative determination of the new anti-psychotic drug ZIP.

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**Abbreviations used:** CID, collision-induced spectra; FIA, flow ionization analysis; ICH, International Conference on Harmonization; ZIP, ziprasidone.

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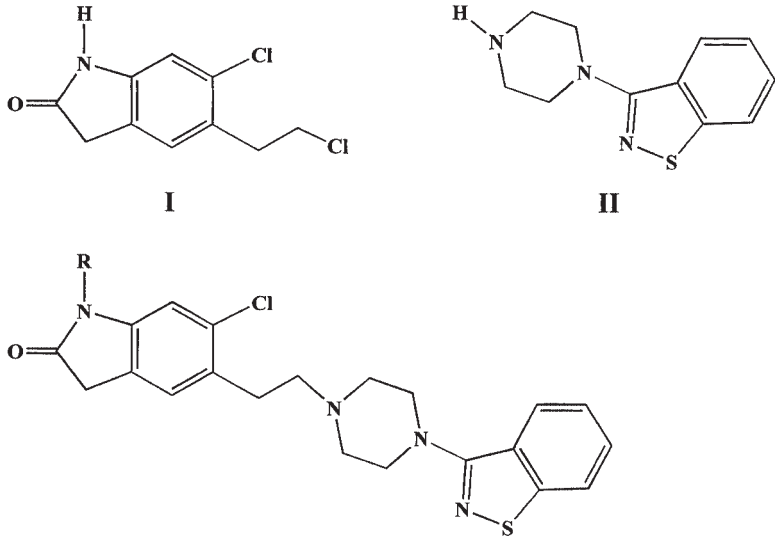


**Figure 1.** The chemical structure of ziprasidone (ZIP) and the three impurities compounds I, II and III.

## EXPERIMENTAL

### Materials and chemicals

Ziprasidone standard and three of ziprasidone related impurities—I (c-89-575), II (cp-78, 459) and III (cp-538-788), the structre of which are shown in Fig. 1—were kindly supplied by Pfizer Egypt. Zeldox® capsules (batch number 01019990), were labeled as containing 40 mg of ZIP per capsule in addition to lactose monohydrate, pregelatinized maize starch and magnesium stearate, which are tablet excipients. HPLC-grade acetonitrile and methanol were purchased from Merck (Darmstadt, Germany). High-purity water was prepared using a Millipore 0.45 μm, white nylon HNWP 47 mm filter. All other chemicals were obtained from BDH chemicals (Poole, UK) and were of analytical-grade quality.

### Apparatus

The HPLC system consisted of a Hewlett Packard series 1100 equipped with a quaternary pump, diode array detector and a manual injector 20 μL loop. The column used was a Lichrosorb $RP_{18}$ (250 × 4 mm, i.d., 10 μm particle size). Also used were an ultrasonic bath J.P. Selecta (Barcelona, Spain), a Shimadzu dual-wavelength lamp flying spot CS 9301 densitomer (Tokyo, Japan), an ultraviolet short-wavelength lamp (254 nm) and silica gel TLC plates 60 $F_{254}$ on aluminum card (20 × 20 cm, 0.2 mm thickness) with a fluorescent indicator, obtained from Fluka (Buchs, Switzerland).

### Chromatographic conditions

**HPLC method.** A prepacked column Lichrosorb $RP_{18}$ (250 mm × 4 mm, i.d., 10 μm particle size) was used at ambient temperature. The mobile phase consisted of water:acetonitrile:phosphoric acid (76:24:0.5 v/v/v) and was pumped at a flow rate of 1.5 mL $min^{-1}$. It was filtered through a Millipore filter 0.45 μm, white nylon HNWP 47 mm and was degassed before use. The elution was monitored at 229 nm. The injection volume was 20 μL.

**TLC densitometric method.** Solutions of the tested substances were applied to silica gel 60 $F_{254}$ TLC plates using a 20 μL pipette. Development of the plates was carried out using normal vertical developing tank previously saturated with the mobile phase for 45 min at ambient temperature. A Shimadzu dual-wavelength flying spot scanner was used for densitometric evaluation of the plates.

**Electrospray–mass spectrometry.** ESI-MS and ESI-MS/MS analyses were carried out on a Micromass QuattroLC benchtop triple quadrupole mass spectrometer (Micromass, UK) fitted with a Z-spray ESI source. The data was acquired in the flow ionization analysis (FIA) mode using a Harvard Model 22 syringe pump connected directly to the ion source via peak tubing. The ESI source temperature was kept at 140°C and desolvation temperature was 250°C. The capillary voltage was maintained at 3.0 kV for negative-ion analysis, at 3.5 kV for positive-ion analysis, and the extraction voltage was 3 V. Nitrogen was used as the nebulizing gas at a flow rate of 110 L $h^{-1}$ and as the desolvation gas at a flow rate of 300 L $h^{-1}$. Argon was used as the collision gas at a pressure of 0.2 Pa.

The resolution of both MS1 and MS2 was maintained at a level that yielded a 10% valley between adjacent ions and 0.7 atomic mass units (amu) peak widths at half height.

The Masslynx software (version 3.5; Micromass) provided with the instrument running under the Windows NT environment was used for instrument control and data acquisition.

All compounds were dissolved in acetonitrile-water (4:1) and analyzed first by FIA-ESI-MS in both positive- and

 

negative-ion modes to find the parent ion and to optimize signal. The parent drug ziprasidone, compound II and compound III favored the positive-ion mode while compound I ionized only in the negative-ion mode. Collision-induced spectra (CID) for the four compounds were then obtained. For ziprasidone the cone voltage optimized to 35 V and collision energy was optimized to 20 eV. For compound II the cone voltage optimized to 25 V and collision energy optimized to 20 eV. For compound III the cone voltage optimized to 35 V and collision energy optimized to 20 eV. For compound I the cone voltage optimized at 25 V and collision energy at 20 eV.

### Stock solutions

Standard ziprasidone stock solution (0.5 mg $mL^{-1}$) was prepared in methanol and stored in standard laboratory conditions in an amber-colored bottle, tightly capped. For the mixed degradation products stock solution, an accurately weighed quantity of each of the three degradation products (I, II and III) was transferred to the same 50 mL volumetric flask dissolved and diluted to volume with methanol (0.125 mg $mL^{-1}$ each).

### Procedures for HPLC method

**Construction of calibration curve.** Accurately measured aliquots of standard ZIP stock solution equivalent to 0.10–5.00 mg of ZIP were transferred into a series of 10 mL volumetric flasks and made up to volume with methanol. An aliquot of 20 µL of each solution was injected under the operating conditions described above using mobile phase, water:acetonitrile:phosphoric acid (76:24:0.5 v/v/v). Detection was carried out at 229 nm and the flow rate was kept constant at 1.5 mL $min^{-1}$. The calibration graph was constructed by plotting peak areas vs concentrations of ZIP.

**Assay of laboratory-prepared mixtures.** Accurately measured aliquots equivalent to 0.5–4.5 mg of ZIP using its stock solution were transferred into a series of 10 mL volumetric flasks. From 10 to 90% of the mixture of degradation products was added using their stock solution, and the flasks were made up to volume with methanol. The process was continued as in the previous section.

**Assay of the pharmaceutical formulation.** A quantity of mixed contents of 20 capsules equivalent to 25 mg of ZIP was accurately weighed and transferred into 50 mL volumetric flask. The flask was half filled with methanol, shaken automatically for 15 min and made up to volume with the same solvent filtered using a 0.45 µm filter. An accurately measured aliquot equivalent to 0.25 mg of ZIP was transferred into 10 mL volumetric flask and made up volume with methanol. The process was completed as above.

### Procedures for TLC densitometric method

**Construction of calibration curve.** Accurately measured aliquots of standard ZIP stock solution equivalent to 0.25–2.50 mg of ZIP were transferred into a series of 5 L volumetric flasks and made up to volume with methanol. Twenty microliters of each solution were applied to silica gel $60F_{254}$ TLC plates (20 × 20 cm) using a 20 µL pipette. Spots were spaced 2 cm apart from each other and 1.5 cm from the bottom edge of the plate. The plate was placed in a chromatographic tank previously saturated for 45 min with a developing mobile phase: chloroform:methanol:glacial acetic acid (75:5:4.5 v/v/v). The plate was developed by a normal vertical developing tank at ambient temperature at 16 cm distance; the spots were detected under a UV lamp (254 nm) and scanned at 247 nm. The calibration curve was constructed by plotting peak areas vs concentrations of ZIP.

**Assay of laboratory-prepared mixtures.** Accurately measured aliquots of standard ZIP stock solution equivalent to 0.25–2.00 mg were transferred into a series of 5 mL volumetric flasks. From 10 to 90% of mixed degradation products were added using their stock solution. The volume was made up to the mark with methanol. The method was followed as in the previous section.

**Assay of pharmaceutical formulation.** A quantity of mixed contents of 20 capsules equivalent to 25 mg of ZIP was accurately weighed and transferred into 50 mL volumetric flask. The flask was half filled with methanol, shaken automatically for 15 min and made up volume with the same solvent and filtered. The method above was followed.

## RESULTS AND DISCUSSION

Drug impurities and degradation products are produced during the synthesis of the bulk materials or improper storage of the drug, which could be due hydrolysis, photolysis or oxidation. The parent drug ZIP and the three degradation products supplied by the manufacturer were subjected to ESI-MS analysis to confirm their purity and also the structure of the degradation products I, II and III (Fig. 1).

The positive-ion ESI-MS spectrum of the parent drug showed a protonated molecular ion at *m*/*z* 413 with the characteristic envelope for the presence of a single chlorine atom on the molecule (data not shown). The CID spectrum of the parent drug [Fig. 2(A)] showed the protonated molecular ion at *m*/*z* 413 and a major fragment at *m*/*z* 194, corresponding to the neutral loss of benziosthiazole–piperazine moiety with charge retention on the indole ring. The two other significant fragments in the spectrum were due to charge retention on the benzisothiazol–piperazine moiety at *m*/*z* 220, and the loss of a neutral fragment of 43 Da from this moiety corresponding to $C_2H_4NH$.

The positive-ion ESI-MS spectrum of compound III showed the protonated molecular ion at *m*/*z* 427 with the characteristic envelope for the presence of a single chlorine atom on the molecule (data not shown). The CID spectrum of compound III [Fig. 2(B)] showed two fragments that were common to ziprasidone, *m*/*z* 177

 

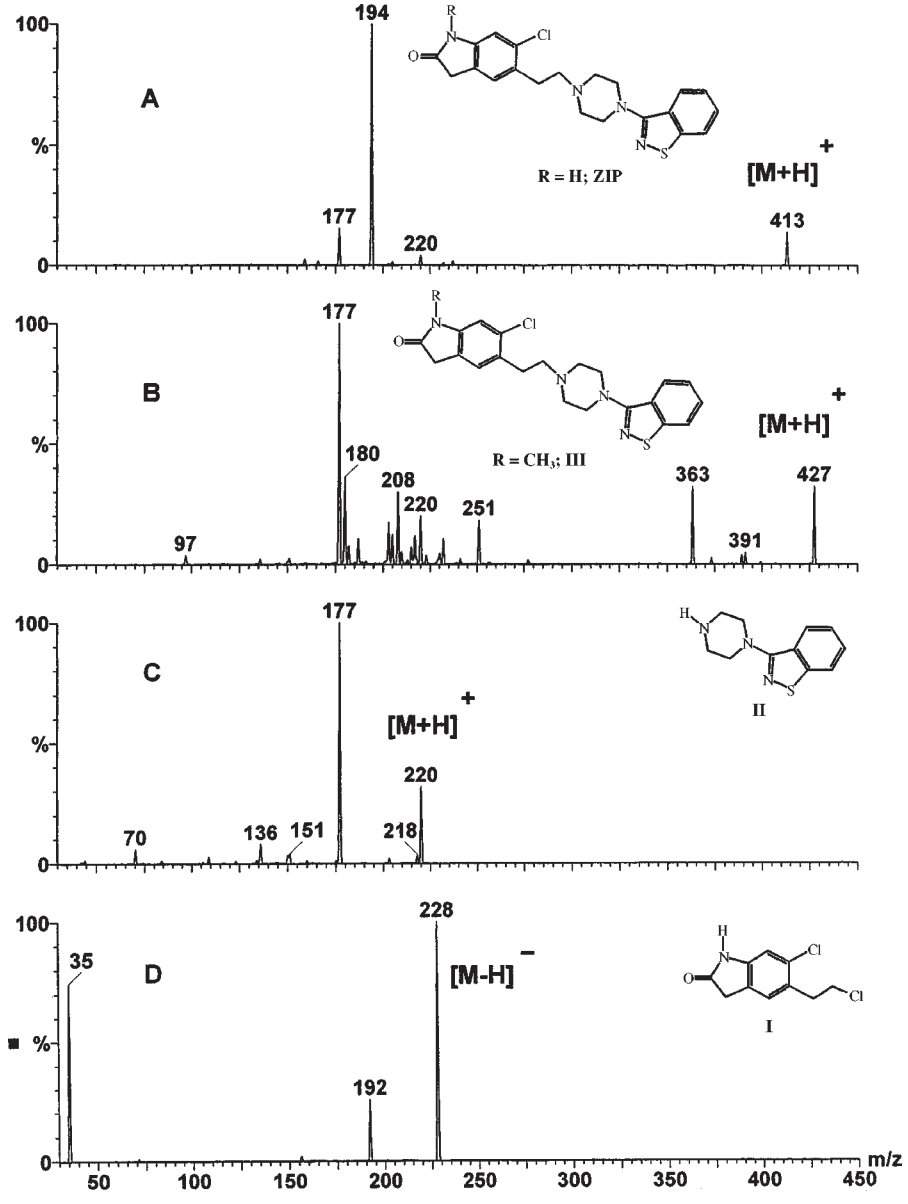


**Figure 2.** The ESI-MS spectra of: (a) ziprasidone; (b) compound III; (c) compound II; and (d) compound I.

and *m*/*z* 220, indicating that this compound has the same benzisothiazole–piperazine moiety as the parent drug. The spectrum also showed a fragment at *m*/*z* 208, which is 14 amu higher than the major fragment of the parent compound. This suggests that compound III has an extra methyl group of the indole part of the molecule, probably an *N*-methyl derivative of ziprasidone.

The positive-ion ESI-MS spectrum of compound-II showed the protonated molecular ion at *m*/*z* 220 with no evidence for the presence of chlorine on the molecule. The CID spectrum of compound II [Fig. 2(C)] showed the protonated molecular ion at *m*/*z* 220 and a major fragment at *m*/*z* 177, which corresponds to the neutral loss of 43 Da. Based on this data and the fragmentation of the parent drug, it is clearly apparent that compound II represents the intact benzisothiazol–piperazine part of the molecule.

The negative-ion ESI-MS spectrum of compound I showed a deprotonated molecular ion at *m*/*z* 228 with the characteristic envelope for the presence of two chlorine atoms on the molecule. The CID spectrum of *m*/*z* 228 [Fig. 2(D)] showed a major ion at *m*/*z* 35 that corresponds to $Cl^-$, and two other fragments at *m*/*z* 192 and *m*/*z* 156 corresponding to loss of one and two HCl moieties, respectively. This data suggests the structures shown in Fig. 1 for the impurities I, II and III.

 

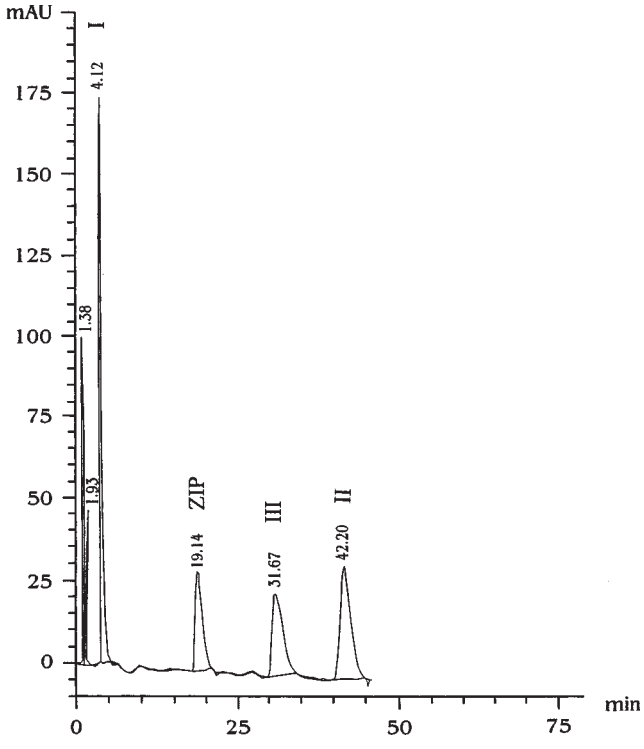


**Figure 3.** A typical chromatogram of ZIP and its degradation products. Retention times of ZIP for compounds, I, II and III three are 19.14, 4.1, 42.20 and 31.67 min, respectively. For chromatographic conditions see Experimental section.

## HPLC method

**Optimization of chromatographic procedure.** Several mobile phases were tried, but the mobile phase composed of water:acetonitrile:phosphoric acid (76:24.0.5 v/v/v) gave satisfactory separation and peak symmetry for ZIP and its degradation products. Increasing the ratio of acetonitrile led to incomplete separation of the drug and its degradation products. Also the increase of the aqueous phase resulted in prolonged retention times. Various reversed-phase columns were used but the Lichrosorb RP-$C_{18}$ column (250 × 4 mm, i.d., particle size 10 μm) gave the minimum elution time with good resolution. A representative chromatogram is shown in Fig. 3. The retention times for ZIP and compounds I, II and III were 19.14, 4.1, 42.20 and 31.67 min, respectively. A linear correlation was obtained between area under the peak and the concentration in the range 10–500 μg $mL^{-1}$ from which the regression equation was calculated:

$$\text{area} = 49.729C - 9.924 \quad r = 0.999$$

where $C$ is the concentration in μg $mL^{-1}$ and $r$ represents the correlation coefficient. The %RSD of the slope and the intercept for the linearity study were 0.192 and 0.113%, respectively. The proposed method was suitable for the determination of ZIP in the presence of 10–90% of mixture of degradation products with mean percentage recovery of 99.80 ± 0.72 (Table 1). All solutions were freshly prepared to ensure stability of the analyte in the solution.

**Table 1. Results of the proposed chromatographic methods (HPLC, TLC) for the determination of ZIP in the presence of its degradation products**

| Sample number | Degradation (%) | HPLC method[a] | TLC densitometric method[a] |
|---|---|---|---|
| 1 | 10 | 100.7 | 99.80 |
| 2 | 20 | 100.5 | 100.20 |
| 3 | 40 | 99.1 | 98.90 |
| 4 | 60 | 100.2 | 100.50 |
| 5 | 80 | 99.7 | 99.89 |
| 6 | 90 | 99.0 | 101.00 |
| Mean (%) | — | 99.80 | 100.00 |
| %RSD | — | 0.718 | 0.712 |

[a] Each result is an average of three experiments.

**TLC densitometric method.** The initial separation was developed using chloroform:methanol (1:1 v/v), then with chloroform:methanol:triethanolamine (15:1:0.1 v/v/v), resulting in the tailing of the spots for the drug and the three degradation products. Subsequently, substituting triethanolamine with acetic acid in ratio of (75:5:4.5 v/v/v) for chloroform:methanol:acetic acid greatly improved the resolution. The tailing for all peaks was reduced considerably. The $R_f$ for values were 0.70, 0.39, 0.18 and 0.35 for ZIP and compounds I II and III, respectively. A linear correlation was obtained between the area under the peak and the concentration in the range 1–10 μg per spot from which the linear regression equation was calculated:

$$\text{area} = 1557.861C + 21.957 \quad r = 0.9998$$

where $C$ is the concentration in μg per spot and $r$ represents the correlation coefficient. The %RSD of the slope and intercept for the linearity study were 0.045 and 0.061%, respectively.

In order to check the applicability of the proposed method as a stability-indicating assay, the intact drug was determined in several mixtures containing different concentrations of the degradation products. Table 1 shows the results of the determination of such mixtures. Satisfactory results were obtained for the recovery of the intact drug, indicating that the two methods are effective for the selective determination of the drug in the presence of a 10–90% mixture of the degradation products, with mean percentage recovery of 100.00 ± 0.71.

Using the previously mentioned parameters, the proposed methods were applied to the analysis of the capsule formulation (Zeldox® containing 40 mg ziprasidone/capsule) as a hydrochloride salt. The results obtained are shown in Table 2 and were found to be in

 

**Table 2. Application of the proposed methods to the determination of pharmaceutical preparation**

| | Zeldox® capsule recovery, percentage ± %RSD | Standard addition ± %RSD |
|---|---|---|
| TLC densitometric method | 99.55 ± 1.83 | 100.78 ± 0.78 |
| HPLC method | 99.25 ± 0.64 | 99.92 ± 0.36 |

**Table 3. Intra- and inter-day variation of ZIP by the proposed methods**

| | HPLC method | | | TLC densitometric method[a] | | |
|---|---|---|---|---|---|---|
| *Inter-day* | | | | | | |
| 0 day | | | | | | |
| Concentration used (μg mL$^{-1}$) | 10.00 | 50.00 | 250.00 | 4.00 | 6.00 | 8.00 |
| $n = 3$ | | | | | | |
| SD | 0.27 | 0.21 | 1.40 | 0.04 | 0.08 | 0.02 |
| %RSD | 0.54 | 2.08 | 0.56 | 0.91 | 1.18 | 0.26 |
| 1 day | | | | | | |
| Concentration used (μg mL$^{-1}$) | 10.00 | 50.00 | 250.00 | 4.00 | 6.00 | 8.00 |
| Percentage recovery | 98.20 | 101.36 | 100.35 | 99.63 | 100.10 | 99.23 |
| $n = 3$ | | | | | | |
| SD | 0.39 | 0.03 | 0.45 | 0.11 | 0.06 | 0.11 |
| %RSD | 0.76 | 0.31 | 0.18 | 2.84 | 0.99 | 1.42 |
| 2 day | | | | | | |
| Concentration used (μg mL$^{-1}$) | 10.00 | 50.00 | 250.00 | 4.00 | 6.00 | 8.00 |
| Percentage recovery | 98.43 | 99.20 | 100.62 | 99.53 | 100.65 | 100.19 |
| $n = 3$ | | | | | | |
| SD | 0.39 | 0.01 | 1.33 | 0.05 | 0.07 | 0.07 |
| %RSD | 0.79 | 0.06 | 0.53 | 1.31 | 1.14 | 0.92 |
| *Inter-day* | | | | | | |
| Concentration used (μg mL$^{-1}$) | 10.00 | 50.00 | 250.00 | 4.00 | 6.00 | 8.00 |
| Percentage recovery | 98.9 | 9.88 | 100.13 | 99.75 | 100.28 | 99.71 |
| $n = 3$ | | | | | | |
| SD | 0.64 | 0.10 | 1.57 | 0.01 | 0.03 | 0.04 |
| %RSD | 1.24 | 1.06 | 0.63 | 0.32 | 0.42 | 0.48 |

[a] Concentration in densitometric method is μg per spot.

close agreement with the claimed content. The results of the two methods were compared statistically with the manufacturer's method using the *t*-test and *F*-test. The calculated value did not exceed the theoretical ones, indicating that there is no significant difference between the proposed methods of analysis with regards to accuracy (*t*-test) and repeatability (*F*-test).

## Validation of the proposed methods

**Accuracy and precision.** The accuracy and precision of the results in term of percent recovery of pure samples analyzed by the proposed methods are shown in Table 3. Interday precisions of the proposed methods were evaluated by assaying freshly prepared solutions in triplicate at three different concentrations. Intraday precisions were evaluated by using freshly prepared solution in triplicate on three different days. These results are summarized in Table 3.

**Specificity.** Specificity is the ability of the analytical method to measure the analyte response in the presence of interferences (degradation products, related substances, excipients). Specificity was checked by adding the degradation products to pure ZIP. Good resolution of ZIP from its degradation products was achieved. The response of the analyte in the mixture was evaluated by the proposed HPLC and TLC densitometric methods showing accurate and precise results (Table 1). Also, in the application of the proposed methods to pharmaceutical formulations, a recovery experiment was carried out by spiking the already analyzed samples of the capsules with three different concentrations of standard ZIP. The percentage recovery ranges obtained by the two methods were 99.0–100.7% and from 98.9–101.0% HPLC and TLC densitometric methods, respectively (Table 3). No interference of the excipients with the peaks of interest appeared; hence the proposed methods were applicable for the

 

**Table 4. Comparison between the results obtained by the proposed methods and the manufacturer's method[a]**

| | HPLC Method | TLC densitometric method | Manufacturer's method[a] |
|---|---|---|---|
| Range of concentration | 10–500 μg per mL | 1–10 μg per spot | 100–350 μg per mL |
| Percentage recovery | 99.71 | 99.26 | — |
| SD | 0.54 | 0.32 | — |
| *n* | 5 | 5 | 5 |
| $F(6.39)$[b] | 1.96 | 5.84 | — |
| $t(2.31)$[b] | 0.343 | 0.8525 | — |

[a] Chromatographic conditions: column, Puresil $C_{18}$ (Waters, 15 cm × 4.6 mm i.d.); mobile phase, $KH_2PO_4$ buffer pH3:methanol (60:40 v/v); flow rate, 1.5 mL $min^{-1}$; temperature, 40°C; detection, UV at 229 nm.
[b] Figures in parentheses represent corresponding tabulated values for $F$ and $t$ at $P = 0.05$.

quantitative determination of ZIP in pharmaceutical dosage forms.

**Sensitivity.** The proposed methods were capable to determine ZIP at low concentration up to 10 μg $mL^{-1}$ and 1 μg per spot for HPLC and TLC densitometric methods, respectively. Therefore the proposed methods are 10-fold and 100-fold more sensitive than the manufacturer's method for the analysis of ZIP (Pfeizer, New York, USA, personal communication), which determined the drug at a validated range of 0.10–0.35 mg $mL^{-1}$ (Table 4).

**Stability of the samples solutions.** The sample solution injected after 1 week at ambient temperature protected from light did not show any appreciable change.

**Limit of detection and limit of quantification.** The limit of detection (LOD) represents the concentration of analyte that yields a signal-to-noise ratio of 3. The LOD for ZIP in HPLC and TLC densitometric method was found to be 0.766 μg $mL^{-1}$ and 165.612 ng per spot, respectively. The limit of quantification (LOQ) represents the concentration of analyte that would yield a signal-to-noise ratio of 10. The LOQ for ZIP in HPLC and TLC densitometric methods was found to be 3.018 μg $mL^{-1}$ and 552.039 ng per spot, respectively.

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