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Multivariate analysis of tioconazole — TCNQ charge transfer interaction: Kinetics, thermodynamics and twofold response optimization

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ABSTRACT

Charge-transfer complex (CTC) formation between tioconazole (TCZ) as an *n*-electron donor and 7, 7, 8, 8-tetracyanoquinodimethane (TCNQ) as a π-acceptor was studied spectrophotometrically with an accompanying kinetic and thermodynamic investigation. Multivariate data analysis via a set of experimental designs was executed for this purpose. A 2^3 - two-level full factorial design (FFD) was used for inspecting the proposed variables while a face-centered central composite design (FCCCD) was used to adjust the levels of variables proved to be significant. Two responses were quantified as a result of this interaction; complex I (Y1, measured at 743 nm) and complex II (Y2, measured at 842 nm). Derringer's function and overlaid contour plots were used to concurrently optimize both responses. Benesi–Hildebrand equation was applied to determine of formation constant (K), and the molar absorptivity (ε) of the formed complex. Different thermodynamic parameters; the standard Gibbs free energy change (ΔG°), the standard enthalpy of formation (ΔH°) and the standard entropy change (ΔS°) were determined for the reaction product. The proposed method was validated regarding the linearity, intra-, and inter-day precision and accuracy, limit of detection, limit of quantification and following the ICH standards. The proposed method was also applied for the determination of TCZ in its pharmaceutical preparations. Having a higher molar absorptivity and higher formation constant, complex II was of choice for all subsequent measurements. Application of Benesi–Hildebrand equation supported the formation of 1: 1 CTC. Thermodynamic study revealed the endothermic characters and the spontaneity of formation of the CTC at high temperature.

1. Introduction

Tioconazole (TCZ), chemically recognizable as 1-[(2*RS*)-2-[(2-chlorothiophen-3-yl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole, Scheme 1 [1], has an unusual antifungal activity against resistant yeast infections with *Candida albicans* [2]. As an anti-fungal, TCZ is commonly used for the treatment of superficial candidiasis and dermatophytoses. Moreover, it is also active against some Gram-positive bacteria [3]. Different techniques were reported for the quantitative analysis of TCZ, including LC [4–12], GC [13], CE [14–16], MS [17], and derivative spectrophotometric methods [18]. Despite being facile, the reported spectrophotometric methods were all, and to the best of our knowledge, based on univariate analysis and are less sensitive compared to the proposed approach. Other chromatographic methods are sensitive and selective but require highly trained and expert operators to perform, beside the high cost, time consumption, and expensive instrumentation needed. This, in turn has led to diminution of their applications in the pharmaceutical analysis and quality control units especially in developing countries.

In this study, a new sensitive spectrophotometric method was developed for quantitative determination of TCZ in pure form and in its pharmaceutical formulations. The developed method was based on the reaction of TCZ with TCNQ to form charge transfer complexes (CTCs) that were measured at 743 nm (intermolecular CTC, Y1) and 842 nm (intramolecular CTC, Y2). A novel approach; factorial design, was used to carefully control the experimental conditions. Such an approach, and in comparison, to the usual one-factor-at-a-time (OFAT) analysis allows having an intimate exploration of the factorial setup, including the factorial levels, their interactions, as well as their momentous impact on the anticipated response [19–21]. Moreover, and with two responses being considered, the proposed approach allowed simultaneous determination of both complexes leading to harmonious conclusions, a concern that cannot be resolved employing the univariate approach [22].

The experimental pattern was inaugurated as two stages. In the first stage; screening, a 2^k-full factorial design (FFD) was implemented. The outcome of this preliminary stage, factors ascertained to be substantial, was transferred into the second stage known as optimization using a face-centered central composite design (FCCCD). Both stages were

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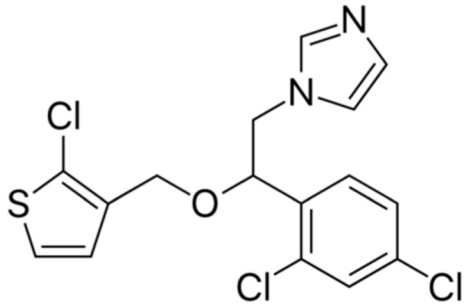


Scheme 1. Chemical structure of tioconazole (TCZ).

accompanied by analysis of variance (ANOVA) at a 95.0 confidence interval (CI) [20,23]. Different thermodynamic parameters were determined for the formed complex as well as the formation constant and the molar absorptivity.

2. Experimental

2.1. Materials and Reagents

All chemicals and reagents were of analytical reagent grade. 7,7,8,8-Tetracyanoquinodimethane (TCNQ) and tioconazole (TCZ) were purchased from Aldrich, USA. Solutions of TCNQ (0.1% and 5 mM) and TCZ (0.2% and 5 mM) were prepared in acetonitrile. Gyno-Trosyd® vaginal tablets (labeled to contain 100 mg TCZ/tablet) and Gyno-Trosyd® vaginal cream (2.0%, labeled to contain 20 mg of TCZ/g of the cream) were products of Pfizer, Egypt and were purchased from local pharmacy stores.

2.2. Apparatus and Software

All spectrophotometric measurements were performed on a Shimadzu UV-1800 spectrophotometer equipped with 10 mm matched quartz cells. A thermostated water bath (WiseBath - fuzzy control system-Wisd laboratory instruments) was used to control the heating temperature.

A Minitab® 17 software was used to build the designs used in screening and optimization steps.

2.3. General Procedures

2.3.1. Procedure for Authentic Samples

Into a series of 10-ml calibrated volumetric flasks, different volumes containing 200–1200 μg of TCZ were added followed by 2.34 ml of 0.1% solution of TCNQ. The contents of each flask were mixed gently, capped, heated in a thermostated water bath at 70 °C for 60 min. Solutions were then cooled to room temperature, diluted to the mark with acetonitrile. Absorbance of the formed CTCs was measured at 743 and 842 nm against a reagent blank prepared similarly omitting the drug.

2.3.2. Procedures for the Kinetic Methods

Different volumes containing 200–1200 μg of TCZ were analyzed as under the general procedure and the absorbance was measured at different time intervals (5, 10, 20, 30, 40, 50 and 60 min).

2.3.3. Procedures for Pharmaceutical Formulations

2.3.3.1. Vaginal Tablets. Ten vaginal tablets were weighed, crushed and finely powdered. An accurately weighed amount of the powdered tablets equivalent to 200 mg of TCZ was dissolved in 20 ml acetonitrile and then filtered through a filter paper moistened with acetonitrile into a 100 ml calibrated volumetric flask. Residue was washed twice with acetonitrile. The filtrate and the washings were completed to volume with acetonitrile to produce a 0.2% solution. Aliquots of the prepared solutions were withdrawn and analyzed as described under the general procedures.

2.3.3.2. Vaginal Cream. Accurately weighed 10 g of the vaginal cream (containing 200 mg of TCZ) was allowed to melt at 70 °C water bath. A volume of 10.0 ml of acetonitrile was added to the melted cream and shacked well. The solution was allowed to cool down, and then the supernatant was filtered through a filter paper moistened with acetonitrile into a 100 ml calibrated volumetric flask. Solidified residue was melted again, and the extraction process repeated twice. The filtrate was completed to volume with acetonitrile to produce a 0.2% solution. Aliquots of the prepared solutions were withdrawn and analyzed as described under the general procedures.

2.3.4. Determination of Stability Constant, Molar Absorptivity and Thermodynamic Parameters

Into a clean dry set of 10 ml volumetric flasks, different volumes (1–6 ml) of 5 mM solution of TCZ were added followed by 1.0 ml of 5 mM TCNQ solution. The content of each flask was well shaken then capped and heated in a thermostated water bath for 60 min at 70 °C. The flasks were then cooled and completed to volume with acetonitrile. The absorbance was recorded at 743 and 842 nm against a reagent blank. The same procedures were repeated at temperatures of 30, 40, 50, and 60 °C.

3. Results and Discussion

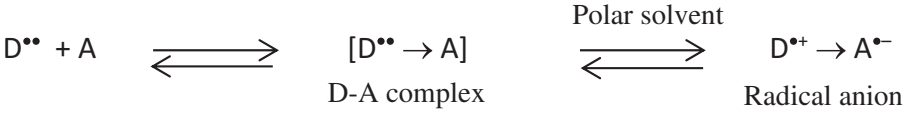
3.1. Charge Transfer Reaction

Exploration of the interaction of TCZ and TCNQ, as shown in Scheme 2, shows that two CTCs were formed. As shown in Fig. 1, the formed greenish colored CTCs were measured at absorption maxima $\lambda_{max} = 743$ and 842 nm. These wavelength bands can be explained considering the predominate radical anion $TCNQ^{*-}$ which is formed as a result of the dissociation of the original donor–acceptor (D–A) complex [24]. This dissociation was accelerated by the high ionizing power of acetonitrile used as a solvent.

3.2. Assessment of the Reaction Conditions

3.2.1. Screening Phase: 2^k — Full Factorial Design (FFD)

Investigating the literature, it was found that the formation of either complex (CTCs in general) is affected by variety of conditions including both 'continuous' and 'categorical' variables. Based on a preceding univariate analysis, three 'continuous' factors; A (volume of TCNQ, TCNQ), B (reaction temperature, Temp), and C (reaction time, RT) were considered in this study. As a preliminary phase, the three factors were fed into Minitab® 17 which was used to assemble the screening design. A 2-level full factorial design (FFD) was the screening design of choice. The experimental pattern as generated by the software had eight runs in the base design plus two central points, amounting to ten experimental



Scheme 2. Proposed mechanism for the charge transfer complex (CTC) formation.