INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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**Review Article**

# A Review on Method Development for Simultaneous Estimation of Itraconazole and Terbinafine in Bulk Drug and Dosage Form

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ARTICLE INFO

Received: 10 April 2024
Accepted: 14 April 2024
Published: 19 April 2024

Keywords:
Itraconazole, Terbinafine, RP-HPLC, UV Spectroscopy, Force Degradation Method Development, Quality by Design, DOE.

DOI:
10.5281/zenodo.10998827

## ABSTRACT

Itraconazole and Terbinafine are widely used antifungal agents with diverse applications in the pharmaceutical industry. The simultaneous estimation of these two drugs in bulk form and dosage formulations is essential for quality control and regulatory compliance. This review comprehensively evaluates various analytical methods reported in the literature for the simultaneous estimation of Itraconazole and Terbinafine. The review highlights the significance of method development in achieving accurate and precise quantification of these drugs. Different analytical techniques such as spectrophotometry, chromatography (high-performance liquid chromatography, ultra-performance liquid chromatography), and capillary electrophoresis have been explored for this purpose. Additionally, various sample preparation techniques including liquid-liquid extraction, solid-phase extraction, and derivatization have been employed to enhance sensitivity and selectivity. Additionally, recent advancements in analytical instrumentation and method optimization strategies are discussed, offering insights into the future direction of method development for simultaneous estimation of Itraconazole and Terbinafine. Overall, this review serves as a valuable resource for researchers and analysts involved in pharmaceutical analysis, providing guidance for the selection and optimization of suitable methods for the simultaneous determination of these important antifungal agents.

## INTRODUCTION

Itraconazole and Terbinafine are widely used antifungal agents with diverse applications in the pharmaceutical industry. The simultaneous estimation of these two drugs in bulk form and dosage formulations is essential for quality control and regulatory compliance. This review comprehensively evaluates various analytical

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**Relevant conflicts of interest/financial disclosures**: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

methods reported in the literature for the simultaneous estimation of Itraconazole and Terbinafine. The review highlights the significance of method development in achieving accurate and precise quantification of these drugs. Different analytical techniques such as spectrophotometry, chromatography (high-performance liquid chromatography, ultra-performance liquid chromatography), and capillary electrophoresis have been explored for this purpose. Additionally, various sample preparation techniques including liquid-liquid extraction, solid-phase extraction, and derivatization have been employed to enhance sensitivity and selectivity. Additionally, recent advancements in analytical instrumentation and method optimization strategies are discussed, offering insights into the future direction of method development for simultaneous estimation of Itraconazole and Terbinafine. Overall, this review serves as a valuable resource for researchers and analysts involved in pharmaceutical analysis, providing guidance for the selection and optimization of suitable methods for the simultaneous determination of these important antifungal agents.

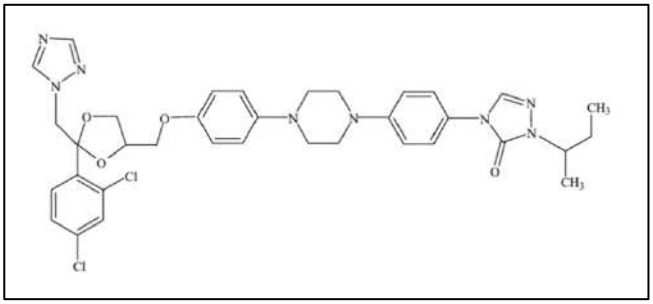

**Figure 1. Chemical Structure of Itraconazole.**

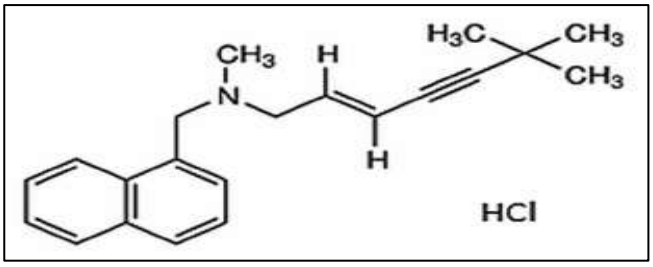


**Figure 2. Chemical Structure of Terbinafine.**

**DRUG PROFILE**

**Table 1: Drug Profile of Itraconazole and Terbinafine.**

| Drug Name | Itraconazole | Terbinafine |
|---|---|---|
| **Category** | Antifungal | Antifungal |
| **Chemical Name** | 4-[4-[4-[4-[[cis-2-(2,4-dichloro phenyl)-2-(1H-1,2,4- triazol-1-ylmethyl)-1,3dioxolan-4-yl] methoxy] phenyl] piperazin-1-yl] phenyl]-2-[(1R1methylpropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one] | (E)-N,6,6-trimethyl-N-(naphthalene- 1-ylmethyl) hept-2-en-4-yn-1 amine |
| **Appearance** | White crystalline powder | White crystalline powder |
| **Chemical Formula** | C35H38Cl2N8O4 | C21H25N |
| **Molecular Weight** | 705.64 g/mol | 291.43 g/mol |
| **Melting Point** | 165 °C (329 °F) | 195°C |
| **Solubility** | Ethanol and water | Ethanol and water |
| **Storage Temperature** | Store in a closed container in room temperature. | Store in a closed container in room temperature. |
| **Solubility** | Ethanol and water | Ethanol and water |
| **Dosage Form** | Tablet, Capsule, creams or Topical solution, Nail Lacquers, Oral suspension. | |

**METHOD DEVELOPMENT AND LITERATURE STUDY IN BULK AND PHARMACEUTICAL DOSAGE FORM:**

**1. Reverse Phase High-Performance Liquid Chromatography:**

Reverse Phase High-Performance Liquid Chromatography is a term that is commonly used to describe liquid chromatography, which consists of a liquid mobile phase that is mechanically pumped through a stationary phase-containing column. An HPLC system consists of an injector, a pump, a column, and a detector [19] . The pump is in charge of regulating the flow of solvent through the system. After leaving the pump, the solvent passes through the injector, then through the section, and then through the optical unit of a detector HPLC columns are made up of spherical silica gel beads coated with the hydrophobic stationary phase and packed into the column. C4 (butyl), C8 (octyl), C18 (octadecyl), phenyl (phenylpropyl), and nitrile (cyanopropyl) columns are common stationary phases [20-24]

**Table 2 – Summary of RP- HPLC method for determination of Itraconazole and Terbinafine:**

| Title | Author | Summary | Reference |
|---|---|---|---|
| Method Development and Validation For Simultaneous Estimation Of Terbinafine & Itraconazole By RP-HPLC Method. | **Yalla Chandana, et, al July 2020.** | **Validation as per ICH Guideline**<br>**Column:** Agilent C18 150 x 4.6mm, 5.0<br>**Mobile phase :** Buffer 0.01N KH2PO4 (4.8pH) : Acetonitrile (60:40v/v)<br>**Flow rate:** 0, 8 ml/min.<br>**Temperature:** 30°C.<br>**Wavelength**:270nm<br>**Retention Time:** Terbinafine and Itraconazole were found to be 2.340 min and 2.940min.<br>**%RSD:** Terbinafine and Itraconazole were and found to be 1.2 and 1.2 respectively.<br>**%Recovery:** 99.56%<br>and 100.16% for Terbinafine and Itraconazole respectively. | **04** |
| Newer RP-HPLC Method Development and Validation for the Simultaneous Estimation of Terbinafine and Itraconazole in Combined Dosage Form. | Kathirvel S et al. December 2019. | Validation as per ICH Guideline<br>Flow rate: 1.0ml/min<br>Wavelength: 250 nm<br>Retention Time: 2.2 Terbinafine and 2.9 min Itraconazole<br>Limit Of detection: 0.95, 2.87 and, 0.24, 0.74µg/ml<br>Limit of quantification: 0.91µg/ml<br>Column: Kromasil C18 (250 ×4.6 mm, 5µm)<br>Mobile Phase:0.01M potassium. Dihydrogen orthophosphate buffer (pH 4): Acetonitrile(50:50 v/v) | **11** |
| Method Development and Validation For Simultaneous Estimation Of Itraconazole And Terbinafine By RP-HPLC Method In Its Pure And Tablet Dosage Form. | C. Vijitha et al, Oct. 2019. | Validation as per ICH Guideline<br>**Flow rate:** 1.6 ml/min.<br>**Wavelength:** 256.0nm.<br>**Retention Time:** Itraconazole and Terbinafine were found to be 2.804 min and 3.875 min.<br>**Limit of Detection**: 0.015 &0.396µg/ml for Itraconazole and Terbinafine respectively.<br>**Limit of Quantification:** 0.045,&1.18µg/ml for Itraconazole and Terbinafine. | **25** |

| | | | |
|---|---|---|---|
| | | **Mobile phase:** Ammonium Acetate and Methanol (35:65)<br>%RSD: 0.99 and 0.42 respectively.<br>**Column:** C18 (150 x 4.6 mm, 3.5m) | |

**UV Spectrophotometric Method:**

The primary idea behind UV spectroscopy states that the excitation of electrons in individual atoms and molecules from lower to higher energy levels is responsible for the absorption of visible and ultraviolet light, or light in the 200–400 nm range [27]. The concentration of the absorbing species in the solution and the path length are proportional to the absorbance of a solution, as per the Beer-Lambert law [28].

Principle: Absorption in the visible or ultraviolet range happens when radiation causes an electronic change within the structure of a molecule or particle. Consequently, the electronic state of the molecules within a sample changes when it absorbs light in the visible or ultraviolet spectrum. Electrons can be promoted from their ground state orbitals to higher orbitals by energy[29].

**Table 3 – Summary of UV Spectrophotometric method for Itraconazole and Terbinafine:**

| Title | Author | summary | Reference |
|---|---|---|---|
| Simultaneous Estimation of Itraconazole and Terbinafine HCl in Bulk and Pharmaceutical Tablet Dosage Form by Using UV Spectrophotometric Method | Akshay G. Deshmukh et al, Sep. 2019. | Validation as per ICH Guideline :<br>UV Shimadzu 1800 model<br>**Solvent.** : acetonitrile<br>**wavelength:** 235 nm was used as λmax for Terbinafine HCl and 263 nm was used as λmax for Itraconazole**.** The percent recovery of Itraconazole and Terbinafine HCl were found to be in the range of 98 – 102 %. | **01** |
| Development and validation of UV spectrophotometric Method for estimation of Itraconazole bulk drug and pharmaceutical formulation | Shalin K. Parikh, et.al April 2011 | Validation as per ICH Guideline:<br>UV Shimadzu 1800 model<br>**Solvent.** : Methanol<br>**Wavelength:** 262 nm was used as λmax for Itraconazole**.** The percent recovery of Itraconazole 99.11- 101.18%, R2) of 0.9982. | **26** |

**Stability-Indicating Method Development And Validation :**

The stability-indicating assay is a verified quantitative technique that aids in the examination of sample stability in the pharmaceutical industry and can identify changes over time by examining the characteristics of drug ingredients and medicinal products. As to the ICH, the aim of a stability-indicating assay method is to precisely measure the intact drug or medications along with

any additional components or excipients and breakdown products. To ensure that there is no peak overlap between the excipients, degradants, and the active medication, it is ideal for every component in the formulation to be present [30,31-33].

**Table 4– Summary of stability Indicating method for Itraconazole and Terbinafine:**

| Title | Author | summary | Reference |
|---|---|---|---|
| Stability Indicating Method Development and Validation for The Estimation Of Terbinafine And Itraconazole In API And Tablet Dosage Form By Rp-HPLC. | **Vankayalapati Manjusha, et.al, May 2021.** | **Validation as per ICH Guideline**<br>**Column:** Phenomenex C18 4.6 x 250mm, 5µm.<br>**Mobile phase :** Buffer 0.01N Kh2po4: acetonitrile (65:35v/v)<br>**flow rate:** of 1.0 ml/min.<br>Temperature 30°C.<br>**wavelength :**270 nm.<br>**Retention time :**Terbinafine and Itraconazole were found to be 2.221 min and 2.819min<br>**%RSD:** Terbinafine and Itraconazole were and found to be 0.8 and 0.9 respectively.<br>**%Recovery:** 100.36% and 100.70% for Terbinafine and Itraconazole respectively. | **02** |
| Stability Indicating RP-HPLC Method For Estimation of Itraconazole and Terbinafine In Bulk And Tablet Dosage Forms | **Kesharaju Shivaranjani, et, al.May 2021.** | **Validation as per ICH Guideline**<br>**Mobile phase:** methanol and water in the ratio of (9.5:0.5v/v)<br>**Column:** Zodiac C18 (250mm x 4.6mm, 5µm)<br>**Flow rate:** of 1mL/min.<br>**wavelength :** 257nm<br>**Retention Time**: Itraconazole and Terbinafine was found to be 4.288 and 2.551 respectively<br>**Linearity :** 10-50µg/mL for both Itraconazole and Terbinafine.<br>**Limit of Detection:** 1.25µg/mL and 8.00µg/mL<br>**Limit of Quantification:** 3.79µg/mL and 24.00µg/mL | **03** |
| Stability-Indicating Method Development and Validation Of Itraconazole And Terbinafine Hcl In Bulk And Pharmaceutical Tablet Dosage Form | **Devyani M Rode, Dr. Nutan Rao, June 2019.** | Validation as per ICH Guideline<br>**Flow rate:** 1.2 ml/min<br>**Wavelength:** 225 nm<br>**Retention Time:** 3.464 min and 8.705 min for Itraconazole and Terbinafine Hcl, respectively.<br>**Run time:** 12 min<br>**Injection volume :** 10 µl<br>**Mobile phase:** acetonitrile and 0.1% triethylamine in the ratio of 90:10<br>**Column:** C18 GIST (250 mm×50 mm, 5 µm) | **05** |
| Stability-indicating rp-hplc method for | **Pushpa d goswami et.al June 2013** | **Validation as per ICH Guideline** | **19** |

| | | | |
|---|---|---|---|
| analysis of Terbinafine Hydrochloride in bulk and in tablet dosage form | | **Column:** Neosphere C18 (250 x 4.6 mm, 5µm)<br>**Mobile phase :** methanol: 0.5% Triethanolamine. 0.5% **flow rate:** of 1.2 ml/min.<br>**Run time** :8 min<br>**Wavelength: 250** nm.<br>**%RSD:** less than 2%<br>**%Recovery:** 100% | |

## CONCLUSION:

The USFDA approved Itraconazole and Terbinafine in 1992.As a result of the above information, it can be concluded that the numerous analytical procedures used to determine simultaneous estimation of Itraconazole and Terbinafine alone or in combination have been successfully utilized on a routine basis, allowing the drug to be quantified in various pharmaceutical dosage forms. These procedures are all simple, fast, accurate, sensitive, and reproducible, with high linearity and precision.

## ACKNOWLEDGMENT:

I would like to express my sincere thanks to Mrs.Hemlata Bhawar Mam and Dr. Santosh Dighe for their valuable guidance and support for this review work.

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HOW TO CITE: Vanita B.Katore, Hemlata S.Bhawar, Nhavale Geeta, Sabafarin H. Shaikh, Mayur S.Bhosale, Rahul Godge, A Review on Method Development for Simultaneous Estimation of Itraconazole and Terbinafine in Bulk Drug and Dosage Form, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 4, 835-842. https://doi.org/10.5281/zenodo.10998827