www.ijarp.com ISSN 2456-9992 Page: 01-10

International Journal Advanced Research Publications

Review Article

Volume: 02
Issue: 04

REVIEW ARTICLE ON IMPURITY PROFILE OF KETOCONAZOLE

***Arunima Aravind V. P., Sadath S.**

Department of Pharmaceutical Analysis, Malik Deenar College of Pharmacy, Seethangoli, Kasaragod, Kerala, India.

Article Received: 09 April 2026, Article Revised: 29 April 2026, Published on: 19 May 2026

***Corresponding Author: Arunima Aravind V. P.**

Department of Pharmaceutical Analysis, Malik Deenar College of Pharmacy, Seethangoli, Kasaragod, Kerala, India.

DOI: https://doi-doi.org/101555/ijarp.2056

ABSTRACT

This review focuses on impurity profiling and analytical characterization of ketoconazole, an imidazole antifungal drug, with emphasis on pharmaceutical impurities, analytical techniques, and forced degradation studies. Pharmaceutical impurities, including organic impurities, inorganic impurities, residual solvents, and elemental impurities, significantly influence the safety, efficacy, and stability of drug products. The study discusses impurity classification according to ICH and USP guidelines, sources of elemental impurities, and the importance of impurity control in pharmaceutical quality assurance and regulatory compliance. Various analytical and characterization techniques such as UV spectroscopy, FTIR, NMR spectroscopy, mass spectrometry, HPLC, TLC, GC, and hyphenated techniques like LC–MS and GC–MS are reviewed for impurity detection and identification. Ketoconazole was selected as the drug of choice, and a validated RP-HPLC method was employed for its analysis and stability studies. Method validation parameters including specificity, linearity, precision, accuracy, robustness, LOD, and LOQ were successfully established according to ICH guidelines. Impurity profiling identified major impurities such as deacetyl ketoconazole, trans-ketoconazole, and 4-nitrophenyl acetate using spectroscopic methods. Forced degradation studies under acidic, alkaline, oxidative, photolytic, and thermal conditions demonstrated that ketoconazole undergoes degradation under stress, with thermal degradation showing the highest impurity formation. The study concludes that impurity profiling and stability-indicating analytical methods are essential for ensuring the quality, safety, and therapeutic effectiveness of pharmaceutical products.

KEYWORDS: Ketoconazole, impurity profiling, Forced Degradation Studies, ICH Guidelines.

INTRODUCTION

Pharmaceutical impurities are the unwanted chemicals that remain with the active pharmaceutical ingredients (APIs) or are developed during formulation or upon aging of both API and formulated APIs to medicines. The presence of these impurities even in minor amounts can influence the efficacy and safety of the drug. Impurities present in excess of 0.1% should be identified and quantified by selective methods. Isolation, identification, and quantification of impurities help us in various ways to obtain a pure substance with less toxicity and safety in drug therapy.

CLASSIFICATION OF IMPURITIES IN NEW DRUG SUBSTANCES, API, NEW DRUG PRODUCT

Authorities classify impurities differently.

As per ICH

In chemical synthesis, the impurities produced can be classified into three classes as follows:

a. Organic impurity (process- and drug-related)

b. Inorganic impurity

c. Residual solvents

a. Organic Impurity:

These impurities may arise during the manufacturing process or storage of the new drug substances, which includes starting materials, by-products, intermediates, degradation products, reagents, ligands, and catalysts.

b. Inorganic Impurity:

These impurities include reagents, ligands and catalysts, heavy metals or other residual metals, inorganic salts, filter aids, charcoal etc.

c. Residual Solvents:

These solvents are organic or inorganic liquids used during the manufacturing process. Since these are generally of known toxicity, the selection of appropriate controls can be accomplished easily. For the detection of residual solvent, gas chromatography is used because they are most volatile in nature. Non-volatile solvents are converted to volatile solvents by chemical derivatization.

Table no.1: Classification of residual solvents As per the United States Pharmacopoeia.

Solvent Class	Risk Assessment	Example
Class I	Solvents to be avoided	Benzene (2ppm), Carbon tetrachloride (4ppm), Methylene chloride (600ppm), Methanol (3000ppm), Pyridine (200ppm), Toluene (890ppm)
Class II	Solvents to be limited	N, N-dimethylformamide (880ppm), Acetonitrile (410ppm)
Class III	Solvents with low toxic potential	Acetic acid, Ethanol, Acetone – permitted daily exposure ≤ 50mg/day

The United States Pharmacopoeia (USP) classifies impurities into two sections i.e. ordinary impurities and organic volatile impurities.

a. Ordinary impurities

b. Organic volatile impurities

a. Ordinary Impurities:

Ordinary impurities are found in bulk pharmaceutical chemicals that are innocuous by virtue of having no significance on the biological activity of the drug substance. These impurities may arise out of the synthesis, preparation or degradation of the chemical.

b. Organic Volatile Impurities:

Organic volatile chemicals are produced in the manufacture of drug substances or excipients or in the preparation of drug products; they are volatile in nature and by themselves get removed out at the time of storage or process.

ANALYTICAL DEVELOPMENT METHOD

Meaningful and reliable analytical data is essential during drug development.

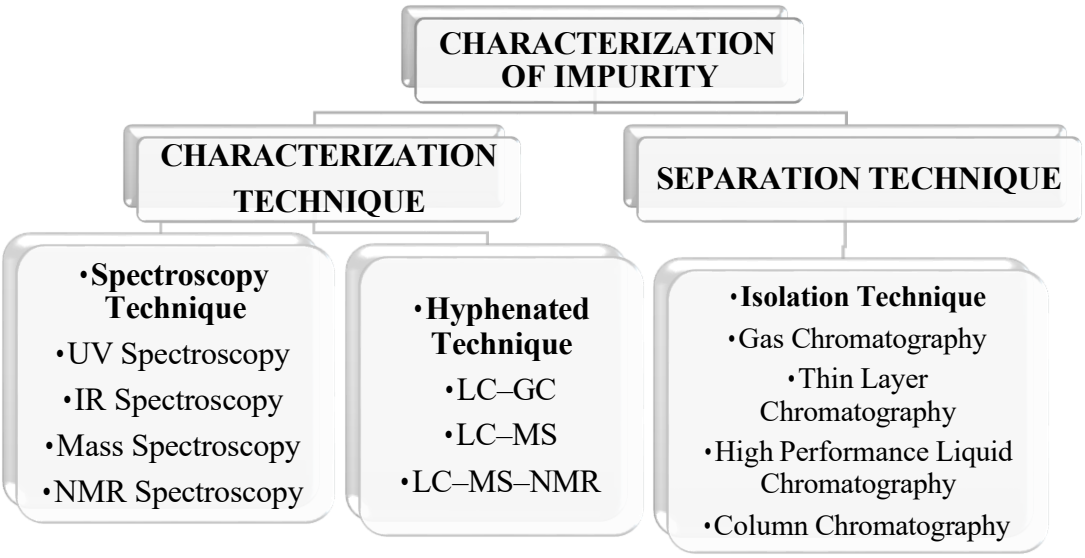
Steps in Analytical Method Development

1. Selection of sample set for method development
2. Screening of chromatographic conditions and phases
3. Optimization of method for ruggedness and robustness

Methods for Identification of Impurities

- Separation methods
- Isolation methods
- Characterization methods
- Reference standard methods

- Spectroscopic methods



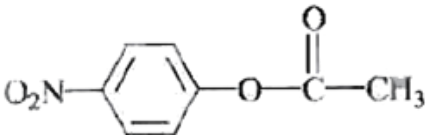
IMPURITY PROFILING OF KETOCONAZOLE

The various type of impurities is present in the drug ketoconazole namely:

a. N-Deacetyl ketoconazole

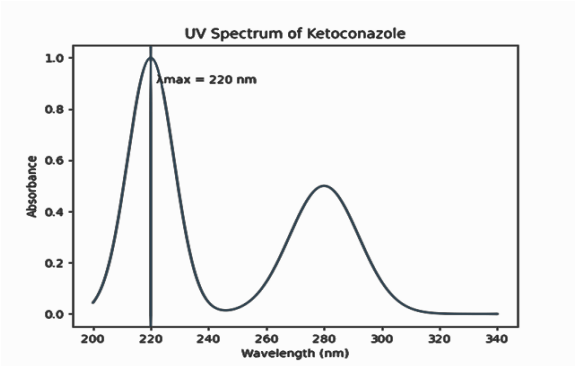
b. 4-Nitrophenyl acetate

c. Trans- ketoconazole

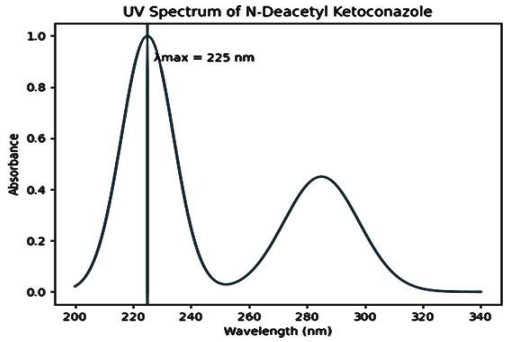


4-Nitro phenyl acetate

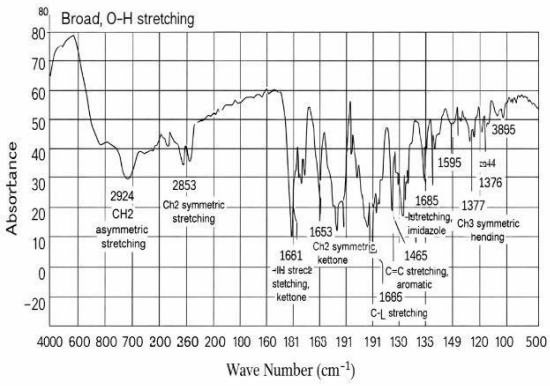
UV SPECTRUM OF KETOCONAZOLE



UV SPECTRUM OF IMPURITY OF N- DEACETYL KETOCONAZOLE

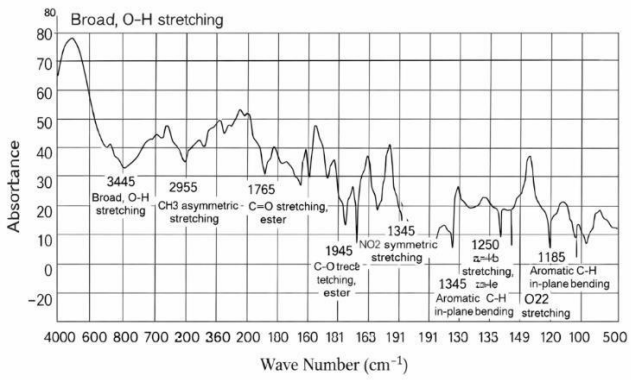


FTIR SPECTRA OF KETOCONAZOLE



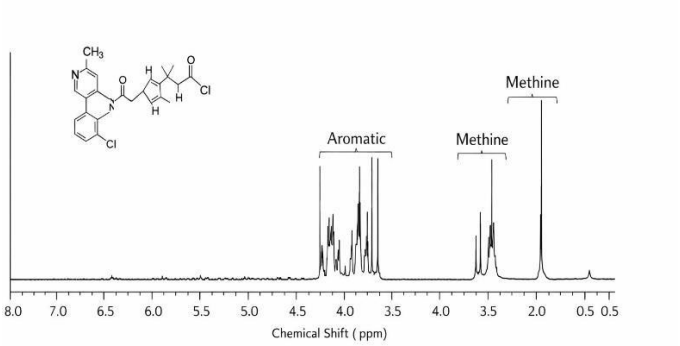
Wave Number (cm⁻¹)	*Vibrational Mode*
3425	*Broad O–H stretching*
2924	*CH_2 asymmetric stretching*
2853	*CH_2 symmetric stretching*
1693	*C=O stretching (ketone)*
1612	*C=N stretching (imidazole)*
1585	*C=C stretching (aromatic)*
1465	*CH_2 bending*
1377	*CH_3 symmetric bending*
1296	*C–N stretching*

FTIR SPECTRUM OF IMPURITY 4 – NITROPHENYL ACETATE



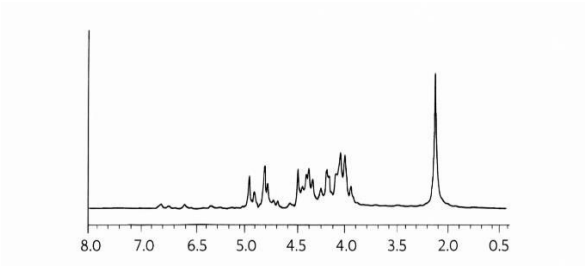
Wave Number (cm^{-1})	Vibrational Mode
3445	Broad O–H stretching
3085	Aromatic C–H stretching
2955	CH_3 asymmetric stretching
1765	C=O stretching (ester)
1525	NO_2 asymmetric stretching
1345	NO_2 symmetric stretching
1250	C–O stretching (ester)
1185	Aromatic C–H in-plane bending
1105	Aromatic C–H in-plane bending

NMR SPECTRA OF KETOCONAZOLE



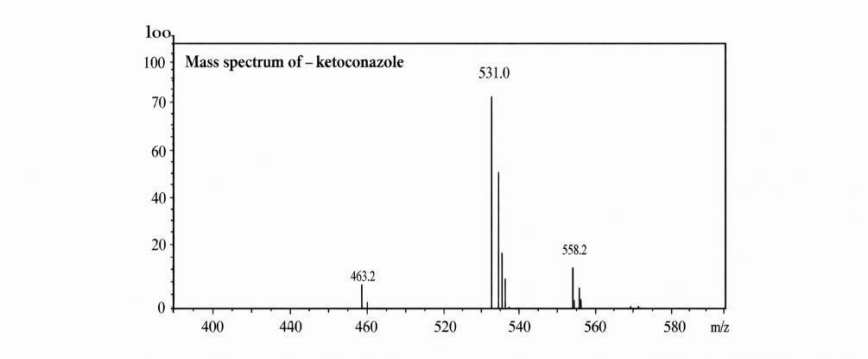
Chemical Shift (ppm)	Proton Type
4.5 – 3.5	Aromatic/CH
~3.3 – 3.0	Methine
~2.2 – 1.8	Methine

NMR SPECTRA OF IMPURITY N-DEACETYL KETOCONAZOLE

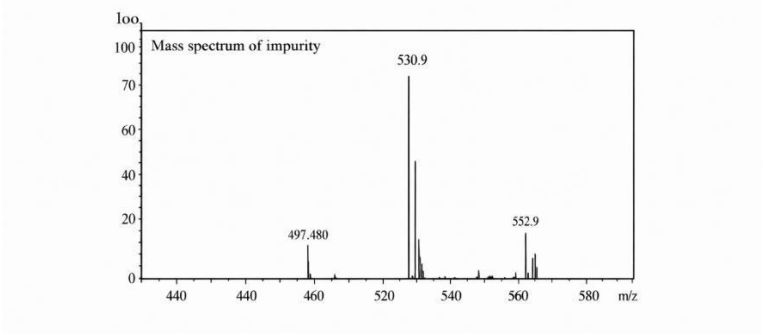


Chemical Shift (δ, ppm)	Multiplicity	Proton Type
~5.2–5.0	Multiplet	Aldehyde proton or alkene proton
~3.5–3.2	Broad	Protons near oxygen
~2.1–2.0	Sharp singlet	Alkyl protons

MASS SPECTRA OF KETOCONAZOLE



MASS SPECTRUM OF IMPURITY TRANS KETOCONAZOLE



FORCED DEGRADATION STUDIES OF KETOCONAZOLE

Forced degradation studies of ketoconazole were carried out under ICH stress conditions using an environmental chamber.

1. Acid Hydrolysis

- Condition: 1M HCl at 60°C, 75% RH for 16 hr
- Procedure:
  - 1 ml stock solution + 1 ml 1M HCl in 10 ml flask
  - After stress, neutralized with 1M NaOH
  - Volume made up with mobile phase

2. Base Hydrolysis

- Condition: 1M NaOH at 60°C for 16 hr
- Procedure:
  - 1 ml stock solution + 1 ml 1M NaOH
  - After stress, neutralized with 1M HCl
  - Volume adjusted with mobile phase

3. Photolytic Degradation

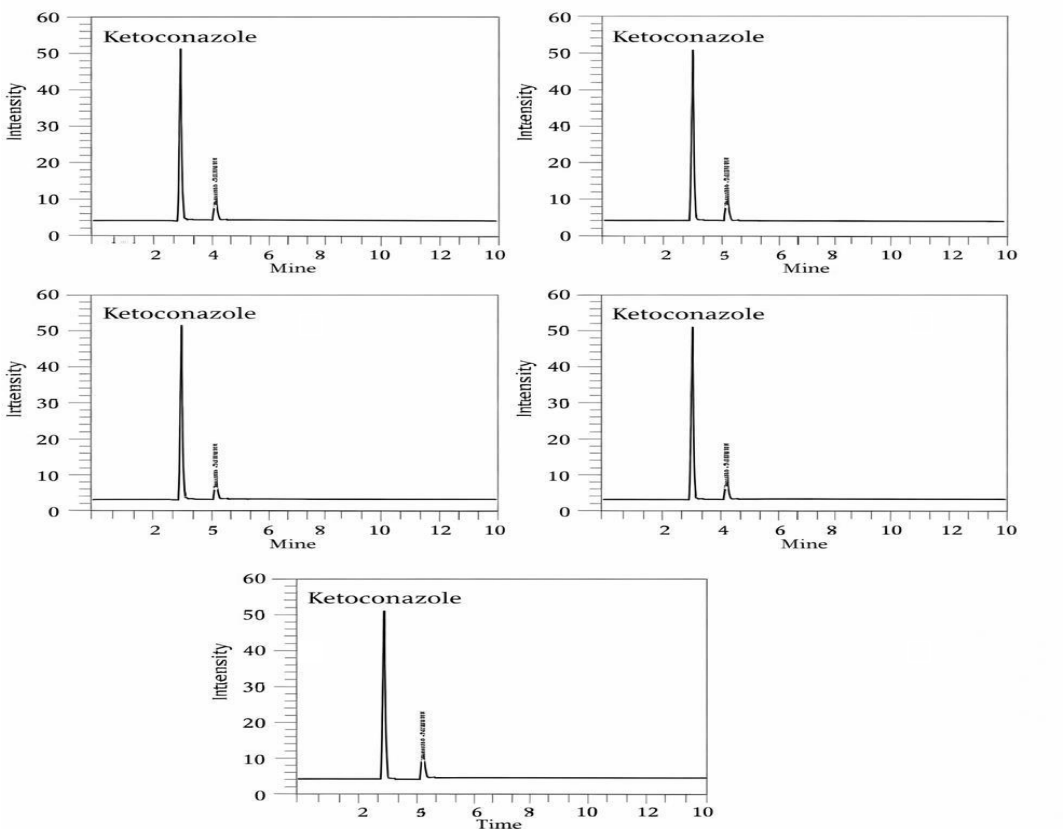
- Condition: Sunlight (60000–70000 lux) and UV light at 254 nm for 48 hr

- Procedure:
  - 1 ml stock solution diluted to 10 ml with mobile phase

4. Oxidative Degradation

- Condition: 6% H_2O_2 at 60°C, 75% RH for 16 hr
- Procedure:
  - 1 ml stock solution + 1 ml 6% H_2O_2
  - Volume made up with mobile phase after stress study

Stress Condition	Time	% Degradation
Acid Hydrolysis (0.1 M HCl)	16 hr	5.13
Base Hydrolysis (0.1 M NaOH)	16 hr	4.80
Photolysis	48 hr	3.56
Oxidation (3% Hydrogen Peroxide)	16 hr	3.95
Thermal (60°C)	16 hr	6.56



Degradation chromatograms of the ketoconazole at various stressed condition. Acidic(A), Alkaline(B), Oxidative (C), Photolytic (D), Thermal (E)

CONCLUSION

The review provides a perspective on impurities in drug substances and drug product. Impurity profiling of pharmaceuticals is receiving an increasing importance and drug safety receives more and more attention from literature. There is strong requirement to have unique specification standards with regard to impurities. Impurity profiling study provides valuable information about the impurity types and classification, sources, WHO and ICH Guidelines and analytical techniques for determination.

The HPLC method for ketoconazole was validated in terms of linearity, accuracy, precision and limits of detection and quantitation. Statistical analysis proved the method enabled reproducible and selective quantification of these drugs as bulk drug and in pharmaceutical dosage forms. Because of the method effectively separates the drugs from their degradation products, it can be used as stability indicating. Impurity profiling was done by UV Spectroscopy, FTIR Spectroscopy, Mass spectroscopy, NMR Spectroscopy. Forced degradation study of ketoconazole was performed and are found degraded at different condition such as acidic, basic, oxidative, photolytic and thermal degradation.

Thermal conditions play a significant role in the formation of impurities, indicating that thermals are one of the key reasons for impurity generation in ketoconazole.

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