Int. J. Sci. R. Tech., 2025 2(11)
A Multidisciplinary peer-reviewed Journal
www.ijsrtjournal.com [ISSN: 2394-7063]

Original Article

Review on Fluconazole: Properties and Analytical Methods for its Determination

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ABSTRACT

Fluconazole is a triazole antifungal drug widely prescribed for systemic and mucocutaneous fungal infections. It acts by inhibiting fungal cytochrome P450-dependent 14α-demethylase, a key enzyme in ergosterol biosynthesis, leading to disruption of fungal cell membrane integrity. Due to its favorable pharmacokinetic profile, including high oral bioavailability and extensive tissue distribution, Fluconazole remains a first-line antifungal therapy. The accurate determination of Fluconazole in pharmaceutical formulations and biological matrices is critical for quality control, pharmacokinetic, and therapeutic drug monitoring purposes. This review highlights the physicochemical properties, pharmacological profile, and a comprehensive overview of analytical techniques employed for its quantification—such as spectrophotometry, HPLC, LC–MS/MS, GC, CE, and electrochemical methods. Each technique is discussed with respect to its principle, analytical performance, sample preparation, advantages, and limitations. Furthermore, recent advancements in miniaturized and high-sensitivity detection systems are emphasized.

Keywords: Fluconazole, Triazole antifungal, HPLC, LC–MS/MS, Spectrophotometry, Analytical methods, Drug quantification, Method validation

INTRODUCTION

Fungal infections have become a significant global health concern, particularly among immunocompromised individuals such as those undergoing chemotherapy, organ transplantation, or living with conditions like HIV/AIDS. Fungi, although a normal part of the human microbiota, can cause opportunistic infections when the immune system is weakened or compromised. The most common fungal pathogens include Candida spp., Aspergillus spp., Cryptococcus neoformans, and Histoplasma capsulatum. These infections range from superficial, affecting the skin, nails, and mucous membranes, to invasive systemic infections that can be life-threatening. The clinical significance of antifungal agents cannot be overstated. Effective antifungal therapy reduces morbidity and mortality in vulnerable populations, prevents the spread of fungal pathogens, and complements other treatment regimens such as antibiotics and immunosuppressive therapies. However, challenges such as drug interactions, toxicity, and resistance demand continuous research and development in antifungal pharmacology, therapeutic monitoring, and analytical methodologies. Fluconazole, a second-generation triazole antifungal agent, was first synthesized in the late 1970s and introduced into clinical practice in the early 1990s. It was developed as an improvement over earlier azoles like ketoconazole, offering better oral bioavailability, broader antifungal spectrum, and fewer adverse effects. The drug's success lies in its unique chemical structure—a fluorinated derivative of the azole ring—which enhances its water solubility and systemic distribution. Therapeutically, fluconazole is widely used to treat fungal infections caused by susceptible organisms. It is effective against various Candida species, including Candida albicans, C. glabrata (with caution), C. parapsilosis, and C. tropicalis, making it a first-line treatment for oropharyngeal candidiasis, esophageal candidiasis, vaginal candidiasis, and systemic candidemia. It is also employed in the treatment and prevention of cryptococcal meningitis, particularly in HIV/AIDS patients, and in the management of fungal infections in immunocompromised hosts. The spectrum of activity of fluconazole is primarily fungistatic rather than fungicidal, meaning it inhibits fungal growth without directly killing the cells. Nevertheless, its favorable safety profile, oral administration, and

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.

extensive tissue penetration— including cerebrospinal fluid—have made it indispensable in both acute and long-term antifungal therapy. Despite its advantages, fluconazole's use must be carefully monitored due to emerging resistance patterns and potential interactions with other drugs metabolized by cytochrome P450 enzymes. The objective of this review is to comprehensively explore the physicochemical properties and analytical methods employed for the determination of fluconazole. Given its extensive therapeutic application, ensuring the quality, safety, and efficacy of fluconazole through accurate and precise analytical techniques is of paramount importance. Understanding the physicochemical properties of fluconazole is essential because these characteristics directly impact its formulation, delivery, stability, and therapeutic action. Properties such as solubility, partition coefficient, melting point, and pKa determine how fluconazole behaves in different environments—whether in the gastrointestinal tract, bloodstream, or targeted tissues. For instance, its high aqueous solubility facilitates oral absorption, while its moderate lipophilicity enables effective distribution across biological membranes. Analytical determination of fluconazole is equally vital in ensuring therapeutic success. Precise quantification techniques are required at multiple stages—from raw material testing to finished product release and post-marketing surveillance. In clinical settings, therapeutic drug monitoring is necessary to avoid toxicity, especially in populations with compromised liver or kidney function. Analytical methods help detect variations in drug concentration, assess pharmacokinetic parameters, and guide dose adjustments. In summary, a deep understanding of fluconazole's properties and analytical determination not only enhances drug development and clinical management but also safeguards patient health and contributes to global efforts against antifungal resistance.

AIM:

The aim of this review is to provide a comprehensive overview of the physicochemical properties of fluconazole and the various analytical methods used for its determination.

OBJECTIVES:

1. To describe the chemical, physical, and pharmacokinetic properties of fluconazole
2. To summarize the mechanisms of action and clinical relevance of fluconazole
3. To review the analytical methods used for fluconazole determination
4. To assess the role of analytical methods in pharmaceutical quality control and therapeutic drug monitoring
5. To identify challenges and areas for improvement in fluconazole analysis
6. To provide insights into future trends and research directions

Analytical Methods for Determination of Fluconazole:

ANALYTICAL METHODS FOR FLLUCOCANAZOLE DE'ERMINATION

Method	Principle	Matrix	Advantages	Limitations
UV-Visible Spectrophotomtry	Absorbance at λmax 260–262 nm	Formulations, plasma	Simple, low cost	Poor sensitivity, interference
HPLC-UV	Reverse-phase chromatography, UV detection	Plasma, formulations	Robust, reproducible	Medium sensitivity
LC-MS/MS	Chromatography co-upled with MS detec-	Plasma, urine, CSF	Highly sensitive, selective	Expensive instrumentation
GC-MS	Requires derivatization, gas-phase separation	Plasma, formulations	High resolution	Complex sample prep
Capillary Electrophoresis	Electrophoretic separation by charge/mass ratio	Plasma	Low solvent use	Reproducibility issues
Microbiological Assay	Redox detection on modified electrodes	Formulations	Portable, rapid	Matrix-dependent
	Inhibition zone/ turbidity	Drug potency test	Measures bioactivity	Low precision, time-consuming

Need of The Work:

1. Ensuring Drug Safety and Efficacy
2. Managing Emerging Drug Resistance
3. Supporting Quality Control in Pharmaceutical Manufacturing
4. Monitoring Therapeutic Drug Levels in Patients
5. Compliance with Regulatory Requirements
6. Advancing Research and Development
7. Protecting Public Health

BACKGROUND OF FLUCONAZOLE:

Development History:

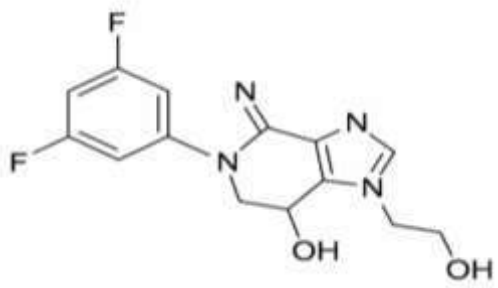
The development of fluconazole was part of a broader scientific effort in the 1970s and 1980s to create safer and more effective antifungal agents. The first generation of azole antifungals, such as **ketoconazole**, was introduced in the late 1970s. While ketoconazole was a breakthrough, it had limitations including poor penetration into the cerebrospinal fluid (CSF), variable bioavailability, and significant hepatotoxicity. These shortcomings drove pharmaceutical research toward the development of a new generation of azoles with improved pharmacological properties. **Fluconazole** was synthesized by scientists at **Pfizer Inc.** in the early 1980s as part of a research initiative to develop a triazole-based antifungal with better efficacy and safety. The compound was designed with the goal of achieving high oral bioavailability, water solubility, reduced toxicity, and reliable CNS penetration. These features were crucial for treating systemic fungal infections, especially in immunocompromised populations such as individuals with HIV/AIDS. The drug underwent extensive preclinical testing followed by clinical trials, and it was **first approved by the U.S. Food and Drug Administration (FDA) in 1990** for the treatment of oropharyngeal and esophageal candidiasis, cryptococcal meningitis, and systemic candidiasis. Its approval coincided with the peak of the HIV/AIDS epidemic, and fluconazole quickly became a critical tool for managing opportunistic fungal infections in affected patients. The success of fluconazole led to the expansion of its approved indications and global use. It became widely available in both oral and intravenous formulations, with oral tablets and suspensions offering treatment flexibility. Its inclusion in the **World Health Organization (WHO) Model List of Essential Medicines** reflects its importance in global public health. In the years following its release, fluconazole became the benchmark against which other antifungals were compared. Its affordability and ease of administration contributed to its widespread adoption, particularly in low- and middle-income countries. However, prolonged use, especially in prophylactic settings, led to increased reports of **antifungal resistance**, prompting further research into newer azoles and alternative antifungal agents. Despite the development of more potent triazoles such as voriconazole, posaconazole, and isavuconazole, fluconazole remains a cornerstone of antifungal therapy due to its safety profile, predictable pharmacokinetics, and extensive clinical experience.

Chemical and Physical Properties of fluconazole:

Chemical Properties

1. IUPAC Name: 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)-2-propanol
2. Molecular Formula: $C_{13}H_{12}F_2N_6O$
3. Molecular Weight: 306.27 g/mol

Structure:



Structural Features:

1. Fluconazole belongs to the triazole class of antifungal agents.

2. It contains two triazole rings that inhibit fungal cytochrome P450 enzymes involved in ergosterol synthesis.
3. The presence of fluorine atoms at the 2 and 4 positions of the phenyl ring enhances water solubility and improves its pharmacological profile.
4. The hydroxyl group (-OH) contributes to hydrogen bonding and solubility characteristics.

2. Physical Properties:

1. Appearance: Fluconazole is a white to off-white crystalline powder.
2. Solubility: Freely soluble in water (> 10 mg/mL), methanol, and ethanol.
3. Melting Point: Approximately 137–140°C.
4. pKa: The pKa is around 1.76, indicating weak acidity, and it remains largely unionized under physiological pH.
5. Partition Coefficient (log P): Approximately 0.5 – 1.0, which reflects moderate lipophilicity and aids in tissue persenetration while maintaining solubility in aqueous environments.
6. Density:1.3 g/cm³.
7. Optical Rotation: Fluconazole is achiral and does not exhibit optical activity.

MECHANISM OF ACTION:

Pharmacokinetics and Pharmacodynamics:

Clinical Trials and Efficacy Studies:

Safety Profile and Side Effects:

Common Adverse Effects

Safety in Special Populations

Contraindication:

Limitations and Challenges:

Cost and Accessibility

Global Regulatory Approvals and Guidelines:

FDA and EMA Approvals

WHO Guidelines

Case Reports

CONCLUSION:

Fluconazole remains one of the most widely used antifungal agents due to its broad-spectrum activity, favorable pharmacokinetic profile, and relatively low toxicity. Its chemical and physical properties—such as high solubility, stability, and moderate lipophilicity—contribute to its effectiveness in treating both superficial and systemic fungal infections. By targeting the fungal cytochrome P450 enzyme lanosterol 14α-demethylase, fluconazole disrupts ergosterol synthesis and compromises fungal cell membrane integrity, making it an essential therapeutic option in clinical practice. his review emphasizes the importance of continued research into fluconazole's properties, mechanisms of action, and methods of analysis, particularly in light of growing resistance and evolving clinical demands. A multidisciplinary approach combining proper stewardship, patient education, surveillance, and innovative analytical techniques is essential to safeguard the effectiveness of fluconazole and improve global health outcomes in the management of fungal infections.

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HOW TO CITE: Dnyaneshwari Gaikwad*, Amol Gayke, Amol Jadhav, Komal Kute, Review on Fluconazole: Properties and Analytical Methods for its Determination, Int. J. Sci. R. Tech., 2025, 2 (11), 582-586. https://doi.org/10.5281/zenodo.17667963