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# Insights on Antifungal Drug - Miconazole Nitrate

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**ABHIRAMI VENKATACHALAM*, HARINI CHOWDARY VADLAMUDI**

*[1*]Acharya & BM Reddy College of Pharmacy, Soldevanahalli, Bengaluru – 560107. India.*

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**ABSTRACT**

Miconazole nitrate, a synthetic derivative of imidazole, is an antifungal agent used in the local treatment of vaginal, nail and skin infections due to dermatophytes. Miconazole has been equally effective in both Candida and dermatophyte skin infections. However, it has been used effectively in chronic skin infections that have not satisfactorily reacted to other agents. It is promising to have initial oral and intravenous miconazole therapy in systemic candidiasis. Miconazole preparations are well tolerated and accepted. A greater understanding of the chemistry and specific mechanism of miconazole is critical to improve strategies and to develop better therapeutics. The purpose of this review is to enlighten the chemistry, pharmacology and the various methods used to enhance the solubility of miconazole. This review also includes the physicochemical properties, a brief about pharmacokinetic profile, disadvantages, drug interaction, uses and administration of miconazole nitrate. An assortment of methods has been developed in recent years that can improve its bioavailability. This article significantly reviews the latest published literature on diverse techniques for enhancing the bioavailability of miconazole.

## INTRODUCTION

Miconazole is a synthetic antifungal imidazole that has been used effectively and safely in the treatment of superficial fungal infections for almost 40 years[1]. Miconazole has a powerful wide range of activities against many species of Candida, including *Candida albicans*[2], *Candida glabrata*[3], *Candida dubliniensis*, *Candida parapsilosis* and *Candida tropicalis*[4]. In addition, miconazole is known to work against several fluconazole resistant Candida species (*Candida albicans*, some *Candida glabrata*). A number of *in vitro* studies have proven the broad spectrum activity of miconazole. Miconazole accessibility provides an option centered upon different topical formulations, wide range of action and reduced resistance. Several latest topical miconazole formulations were used to treat oral candidiasis, including buccal tablets, chewing gum, oral gel, and lacquer[5]. The incidence of fungal infections of skin is escalating throughout the world. Around 40 million people have been suffering from fungal infections. With the fungal infections immune system functioning will get hindered which makes a promising progression in the disease. Dermatophytes and candidal infections are the most frequent fungal infections affecting skin[6].

Of a cluster of approximately 100,000 fungi, only a minority of them are pathogens occasionally contaminating, colonizing and infecting human skin[7]. Recent surveys on fungal infections estimate that more than one million individuals died per year particularly those triggered by the species Candida, Cryptococcus and Aspergillus[8]. There appears to be an increase in endemic fungal infection induced by *Blastomyces dermatitidis, Coccidioides immitis/posadasii* and *Histoplasma capsulatum*. Infections like aspergillosis, fusariosis, mucormycosis and candidiasis (health care associated diseases) have been environmentally acquired[9].

The treatment of superficial fungal infections may be accomplished with topical antifungal agents and/or with orally administrated agents. Clotrimazole, econazole, miconazole, terbinafine, fluconazole, ketoconazole, amphotericin, echinocandins, flucytosine and amphotericin are common antifungal medicines. Topical antifungal agents have been administrated as antifungal ointments, creams, gels, sprays and lotions. In addition, antifungal medication can be given orally and IV route[10]. Global warming worsening opens a Pandora box for fungal diseases[11].

**Physicochemical Properties of Miconazole**

Miconazole 1-[2,4-dichloro-b-(2,4-dichlorobenzyl oxy)phenetyl]nitrate exhibits a unique pharmacological activity and exerts a unique multipronged activity against the most important and frequent pathogens responsible for dermatomycoses. It is classified as a broad-spectrum antimycotic and as an active compound against Gram-positive bacteria. Miconazole activity is increased by photodynamic therapy[12]. Miconazole demonstrated very high resistance to crystallization when cooling from the isotropic melting (very high ability to form glass), as well as on heating from glass to the melting temperature (very high stability of glass).

Miconazole's molecular structure is such that it is not able to form hydrogen bonds between the molecules. However, on the other hand, the chlorine atoms present in the miconazole is bulkier and less electronegative in comparision with the voriconazole fluorine. It is likely to inhibit the stacking of the crystal and weaken the dipolar interactions between the molecules, which explain the strong resistance to miconazole crystallization[13].

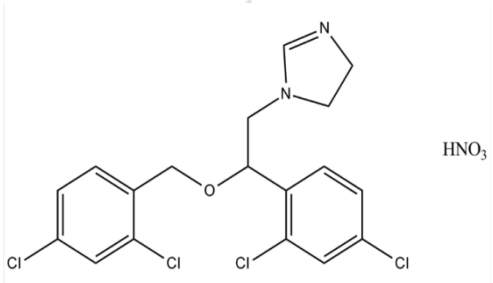


**Figure No. 1: Chemical structure of Miconazole**

**Pharmacokinetics of Miconazole**

**Mechanism of action**

Humans coexist with microbes and an infection develops which elicits body's response when the defense system is damaged or pathogen concentration is exceptionally high[14]. Azoles have limited use for systemic infections, but are commonly used topically for mucosal or skin infections[15]. Imidazole interacts with cytochrome P450 (CYP450) complex to inhibit ergosterol biosynthesis. The production of this enzyme is regulated by the ERG11 gene. Imidazoles inhibit the CYP450 complex's 14a-lanosterol demethylase, an enzyme that converts lanosterol to ergosterol. Inhibition of lanosterol demethylase results in the

replacement of ergosterol by methylated sterols in the plasma membrane. Ergosterol is the fungal cell walls main sterol. It is a vital compound for the growth of cells[16,17].

In general, antimycotic drugs interfere with fungi's life cycle of by inhibiting one or more vital cell functions. Miconazole may harm fungal cell membrane integrity, change fungal attachment and inhibit germ tube and mycelia formation[18]. There appears to be an increase in endemic fungal infections induced by *Histoplasma capsulatum, Blastomyces dermatitidis* and *Coccidioides immitis/posadasii*. Infections like aspergillosis, fusariosis and mucormycosis, and healthcare-associated infections such as candidiasis have been environmentally acquired. The integrity of cell membrane is compromised by sterol precursor accumulation and ergosterol reduction resulting in defective cell membranes, cell budding and enlargement. As a result cell division is hindered, making fungal membranes more permeable and fluid. Azoles cause massive cell membrane destruction resulting in leakage of potassium and sodium ions, as well as low molecular weight phosphates and proteins from the cell[19].

For an antifungal agent to reach the fungus, it must penetrate and remain in the infected portion of the skin. A small lipophilic molecule is likely to be well suited to achieve this goal[20]. The presence of negative charged protein residue and selective membrane ion pumps allows the cells of epithelial in the different tissues, including the skin, to bear a negative charge. Therefore, all the epithelial cells are limited to positively charged solutes[21]. Enhanced drug permeability and sustained pharmacological effect is to result in a positively charged delivery system which interacts powerfully to the cells. Azoles prevent the growth of fungi (fungistatic) and are fungicidal at high levels only[22].

While there are several explanations for the rise in fungal infection, one of the major risk factors for invasive fungal infection is the host immune alteration and the immune modifiers used to combat numerous chronic inflammatory diseases.[23] The management of most superficial and circumscribed cutaneous mycoses may begin with topical agents. To be efficacious, this type of treatment must basically prevent the hyphae invasion of the stratum corneum. To achieve this goal, there is a limited of potential targets for drug action against most fungi [24].

According to the structure and functions of the fungal molecular targets, some antimycotic agents possibly exert fungicidal activity following specific subcellular organelle destructions.

By contrast, other antifungals are fungistatic acting preferentially or distinctively against restricted set of fungal species[25].

**Uses and administration**

Miconazole nitrate chemically is an imidazole also supplied intravenously by infusion for disseminated fungal infections therapy. The drug may be administrated by mouth in a dose of 20 mg/g or as oral gel in case of oropharyngeal and intestinal candidiasis. The typical adult dose is 5-10 ml four times a day. The drug may be used directly as an oral lesion. Miconazole may also be given once daily as a mucoadhesive buccal tablet containing 50 mg miconazole for the treatment of oropharyngeal candidiasis in immunocompromised patients.

Miconazole nitrate is commonly used twice daily for fungal infections treatment of skin as a 2% cream, lotion or powder. The medication is also used for vaginal candidiasis therapy, 5g of 2% intravaginal cream is applied once in a day for 10-14 days or twice in a day for 7 days. Miconazole pessaries may be inserted once daily (100mg) for 7-14 days, twice in a day (100mg) for 7 days, daily (200 or 400mg) for 3 days or a single dose of 1200 mg. Based on the sensitivity and severity of the fungal infection doses have ranged from 0.2 g daily to 1.2 g may be given intravenous thrice in a day. It must b diluted in 0.1 % sodium chloride or 5% glucose and be given by slow infusion. The manufacturers recommend diluting daily dose up to 2.4 g to mg per ml and infused at a rate of 100 mg/h to minimize toxicity.

Recommended dose among neonates is 1ml 2-4 times daily. Children aged 4 months to 2 years may receive 1.25ml 4 times daily; 20-40 mg/kg body may be given over the age of 1 year. And for 2-6 years of age 120 mg twice daily; from 2 years of age 2.5ml can be given 4 times daily; 120mg cab be given four time daily to children aged 6 years. A sustained release lacquer is available for dentures weight daily but at each infusion, no more than 15 mg/kg of drug should be given[26].

**Miconazole Nitrate Pharmacokinetics**

Absorption- Minimal systemic absorption on skin upon topical application. Small amount is absorbed systemically on intravaginal administration.

Distribution-Distributed into body tissues, joints and fluids; poor penetration into sputum, saliva, urine, and CSF.

Metabolism- In the liver, Hepatic Microsomal Enzymes, possible increased plasma concentrations.

Elimination -Intravaginal administration urine and feces (1% of dose) Feces (~50%); urine (<1%, unchanged)[27,28].

**Antifungal agents and Formulations available**

Some common antifungal medicines are clotrimazole, econazole, miconazole, terbinafine, fluconazole, ketoconazole, amphotericin, echinocandins Flucytosine and amphotericin. Topical antifungal agents have been administered as antifungal ointments, creams, gels, sprays and lotions. In addition, antifungal medication can be given orally and IV route.

**Physicochemical property / Drug summary/profile**

| **Physicochemical properties** | **Miconazole nitrate** | **References** |
|---|---|---|
| Chemical formula | $C_{18}H_{14}Cl_4N_2O.HNO_3$ | 29 |
| Chemical name | 1-[2-(2,4-dichloro-phenylmethoxy)-2-(2,4-dichlorophenyl)ethyl}-1H-imidazole nitrate | 29 |
| Category | Antifungal | 29 |
| Description | A white or almost white, crystalline microcrystalline powder | 29 |
| Melting point | 159-163 | 29 |
| Molecular weight | 479.2 | 29 |
| PKa | 6.1 | 30 |
| Log P | 6.1 | 29 |
| Solubility | Quiet highly soluble in water, moderately alcohol soluble, sparingly soluble in methyl alcohol | 29 |
| Half-life elimination | Multiphasic degradation: Alpha: 40 minutes; Beta: 126 minutes; Terminal: 24 hours | 29 |
| Protein binding | 91% to 93% | 29 |
| Interactions | Weak inhibitor of CYP2C9 | 31, 32 |
| Optical rotation | -0.10 to +0.10 | 31, 32 |
| Phase | Launched | 31, 32 |
| Indication | Fungal infections | 31, 32 |
| Pharmacological description | Sterol demethylase inhibitor, cell wall synthesis inhibitor | 31, 32 |
| Sulphated ash | Not more than 0.1% | 31, 32 |
| Loss on drying | Not more than 0.5% | 31, 32 |
| Storage | Store protected from light and moisture | 31, 32 |
| Adverse effects | Irritation, burning, itching | 33, 34 |
| Contradictions | Miconazole is contraindicated to cause hypersensitivity to either miconazole or any ingredient in the formulation. | 35 |
| Drug Interactions | With progesterone antifungal agents (Vaginal) may decrease progesterone's therapeutic effect. With vitamin K antagonists (eg, warfarin) topical miconazole may increase the vitamin K serum concentration | 35 |

**Unmet needs / Disadvantages**

Azoles have short half-lives and are known to cause adverse effects such as local irritation, burning sensations, and erythema, rash and skin tenderness. Microwave aided technique of microemulsion in the development of solid lipid nanoparticles filled with miconazole nitrate and econazole nitrate[36]. Adverse reactions are rare and consist primarily of discrete burning, itching, stinging and erythema of the treated site. The vast majority of these reactions are indeed caused by the vehicle components rather than induced by MCZ. A few cases were reported involving MCZ itself and an 'ortho-chloro cross sensitivity' with isoconazole, tioconazole and oxiconazole. In addition, cross-sensitivity of MCZ was shown with ketoconazole and sertaconazole. A few drug-drug interactions were reported with topical MCZ31, particularly with coumarins[37-39].

**Techniques of solubility enhancement [40]**

Solubilisation of drugs is a commonly faced challenge in screening of new chemical entities as well as in formulation designing and development. Solubility is related to therapeutic effectiveness and systemic availability. Therefore, numerous approaches have been explored to increase solubility and dissolution rate of poorly water soluble drugs.

**CHEMICAL MODIFICATIONS**

**Salt Formation:**

It is one of the most common and effective method of increasing solubility for acidic and basic drugs (like aspirin, theophylline, barbiturates).

**Co-crystallization:**

Co-crystals may be denoted as crystalline material or molecular complexes that consist of two or more neutral molecular species associated by non-covalent forces. It can be formed by evaporation of a heteromeric solution or by grinding the components or by sublimation, growth from the melt slurry preparation. It is new approach and an alternative, particularly for neutral compounds.

**Co-solvency / Solvent blending:**

It is recognized that the addition of an organic co-solvent to water can intensely change the solubility of drugs. Weak electrolytes and nonpolar molecules have poor water solubility and it can be enhanced by altering the polarity of the solvent. The solvent used to increase solubility is known as co-solvent.

**Hydrotropy:**

It describes to intensify solubility in water because of large amount of additives. It increases solubility by complexation involving weak interaction between hydrophobic agents (Sodium benzoate, sodium alginate, and urea) and solute.

**Solubilising Agents:**

Solubilizing materials may possibly advance the solubility of poorly soluble drug.

**Nanotechnology Approaches**

It refers to the use of materials and structures at the Nano-range (100 nm or less).

**PHYSICAL MODIFICATIONS**

**Particle Size Reduction:**

The methodologies of size reduction using various milling processes are well established and these practices are a standard part of formulation development. As it results in decreased particle size and the total surface area of particle increases with subsequent increase in solubility.

**Modification of Crystal Habit:**

Polymorphism is the ability of an element or compound to crystallize in more than one crystalline form. These are chemically identical, but they exhibit different physicochemical properties. Likewise, amorphous form of drug is always more apt than crystalline form due to higher energy associated and increase in surface area. Order for dissolution of different solid forms of drug, are- Amorphous >Metastable polymorph >Stable polymorph.

**Complexation:**

It is the association between two or more molecules to form a non-bonded entity with a well defined stoichiometry. Complexation depends on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions. EDTA, EGTA, and cyclodextrins are some of the complexing agents.

**Solubilisation by Surfactants:**

Surfactants are molecule with unique polar and nonpolar sections. The polar group can be anionic, cationic, zwitterions or non-ionic. When small polar molecules are added they can accumulate in the hydrophobic core of the micelles. The principle involved is that surfactant might lower the surface tension and increases solubility of drug.

**Temperature**

Mostly, an increase in the temperature of the solution increases the solubility of a solid solute. For gaseous solutes, an increase in pressure results in increased solubility. For solids and liquid solutes, change in pressure has practically no effect on solubility.

**Nature of the Solute and Solvent**

The amount of solute dissolved in appropriate solvent at room temperature may vary depending in their nature.

**Molecular Size**

Greater the molecule size or higher molecular weight confirms less solubility of the molecule. In organic compounds, the quantity of carbon branching will increase the solubility since more branching will reduce the size of the molecule making it easier to solvate the molecules with solvent.

**Polarity**

Generally, non-polar solute molecules dissolve in non-polar solvents and polar solute molecules dissolve in polar solvents. The polar solute molecule has a positive and negative end. If the solvent molecules are polar then positive end of solvent molecules attract negative end of solute molecules. This is a type of intermolecular force known as dipole-dipole

interaction. Molecules may also have an intermolecular force much weaker than the London Dispersion forces where the positive nuclei of the atoms of the solute molecule will attract the negative electrons of the atoms of a solvent molecule. This provides the non-polar solvent a chance to solvate the solute molecules.

**Polymorphs**

The capacity for a substance to crystallize in more than one crystalline form is polymorphism.

Enantiotropism is the phenomenon where the change from one polymorph to another is reversible. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs show different solubility. Generally, the range of solubility between different polymorphs is only 2-3 folds due to relatively small differences in free energy.

**Rate of Solubilization**

The rate of solubilization is a measure of how fast substances dissolve in solvents.

**Methods of Choice**

**Solid Dispersions:**

It is a group of solid products enclosing at least two different components, typically a hydrophilic matrix and a hydrophobic.

**Complexation:**

Complexation is the association between two or more molecules to form a no bonded entity with a well-defined stoichiometry. Complexation depends on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions.

**Strategies used for enhancing the bioavailability of Miconazole nitrate**

Hydrotropic solubilization method can be used to boost the solubility of poorly water-soluble Miconazole drug. Sodium benzoate, niacinamide, and urea were the hydrotropes selected for the solubility enhancement of drugs. Results exhibited significant increase in aqueous solubility of miconazole in presence of large concentration of hydrotropes[41]. Miconazole

nitrate based solid lipid nanoparticles were prepared by hot homogenization/ultrasonication. Precirol ATO5 as a solid lipid showed highest partition coefficient of 14.6. As Precirol ATO5 has longer-chain fatty alcohol in its structure than the other lipids which might result in the creation of a less ordered solid lipid matrix, leaving enough space to accommodate the drug molecule. Precirol ATO as a core lipid for the MN-SLN formulations could probably enhance solubility[42].

Ternary mixture consisting of miconazole nitrate, Tween 20, Tween 80 and ethanol showed enhanced aqueous solubility of MN from 110.4 to 57,640.0 g/ml which transformed the solubility category of miconazole nitrate from very slightly soluble to soluble[43]. Binary mixtures such as solvent deposition, inclusion complexation and solid dispersion were adopted to enhance solubility using different polymers like lactose, beta cyclodextrin and polyethylene-glycol 6000, respectively. An excellent solubility enhancement, i.e. up to 72 folds and 316 folds of MN was comprehended by binary and ternary mixture, respectively. Solubility enhancement by binary mixtures is achieved possibly due to surface modification and by increasing wettability of miconazole nitarte[44].

Solubility of the spray- or freeze-dried nanosuspension of miconazole nitrate was boosted in presence of mannitol or microcrystalline cellulose (drug substance: excipient ratio of 1:1, w/w), in comparison to the coarse drug suspension (twice the amount dissolved after 10 and 20 min) [45].

Miconazole loaded nanostructured lipid carriers dispersion prepared showed that the developed NLC dispersion presented particles in the nanometric size range, low PI values, good physical stability and with efficient ability for the encapsulation of miconazole[46].

Appropriate selection of components is critical to formulate an efficient nanoemulsion. Low-molar-volume oils like Captex200M for miconazole nitrate are desirable instead of high molar-volume oils, as they typically show better solubilization of the drug[47]. Solid Dispersions of miconazole nitrate, with a water soluble polymer and a super disintegrant prepared by common solvent and solvent evaporation methods employing methanol as solvent showed improved properties. The solid dispersions with combined carriers provided much higher rates of dissolution than super disintegrants alone. Super disintegrants alone or in combination with PVP could be possibly used to improve the dissolution rate of poorly soluble drug miconazole nitrate[48].

Propylene glycol phospholipid vesicles of miconazole nitrate have been advocated as flexible lipid vesicles for enhanced skin delivery of drugs[49]. Intrinsic dissolution tests showed that the formation of salts and cocrystals improved the dissolution rate of miconazole[50]. Inclusion complexes were then prepared by different methods, i.e., kneading, co-evaporation, spray-drying, and lyophilization. The method of preparation of the inclusion complexes in the solid state was shown to greatly affect the properties of the formed complex[51].

Mucoadhesive patches containing of miconazole nitrate were prepared with ionic polymers, sodium carboxymethyl cellulose and chitosan, or non-ionic polymers, polyvinyl alcohol, hydroxyethyl cellulose and hydroxypropylmethyl cellulose. Optimum release behaviour was shown with patches containing 10% w/v PVA and 5% w/v PVP[52]. When hydrogenated phosphatidylcholine (HPC) was added to mineral oil and heated to 95 °C, the solubility of MCZ increased in proportion to the HPC concentration[53].

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