# Fluconazole and its interaction with metal (II) complexes: SEM, Spectroscopic and antifungal studies

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**Abstract**: The human digestive tract contains some 100 trillion cells and thousands of species of micro-organisms may be present as normal flora of this tract as well as other mucocutaneous junctions of the body. Candida specie is the most common organism residing in these areas and can easily invade the internal tissues in cases of loss of host defenses. Modifications of previously existing antifungal agents may provide new options to fight against these species. Inorganic compounds of different antifungals are under investigations. Present study report six complexes of fluconazole with Cu (II)), Fe(II), Cd(II), Co(II), Ni(II) and Mn(II) have been synthesized and characterized by elemental analysis, IR, UV and H-NMR. The elemental analysis and spectroscopic data were found in agreement with the expected values as the metal to ligand value was 1:2 ratios with two chlorides in coordination sphere. The morphology of each complex was studied using scanning electron microscope and compared with fluconazole molecule the flaky-slab rock like particles of pure fluconazole was also observed as reported earlier. However, the complexes of fluconazole were showed different morphology in their micrograph. Fluconazole and its complex derivatives have also been screened *in vitro* for their antifungal activity against *Candida albican* and *Aspergillus niger* by MIC method. The complexes showed varied activity ranging from 2-20%.

**Keywords**: *Candida, Aspergillus,* triazoles, SEM.

## INTRODUCTION

*Candida albicans* is a saprophytic microorganism that is normally found in skin and various mucus membranes in healthy individuals because all humans are colonized with *candida* species, alterations in natural human flora, loss of intact mucocutaneous membranes, leukopenic conditions and decreased cell-mediated immunity may predispose a human to fungal infection (Jonnalagadda *et al*., 1996).

Candida is a very special organism specie as it can manipulate inflammatory responses as needed (Beauséjour *et al*., 1998) and inflammatory responses can have systemic effects (Mark, 2009; Webster and Crowe. 2006; Claveau *et al*., 2004). According to senet, pathogenic behavior of candida may appear following even a minor modification of the host (Senet, 1997).

Although most of the candidial infections effect dermal appendages and mucocutaneous junctions and involve *Candida albicans*, however, in patients who have severely compromized host-defense mechanisms or are on long term intravenous therapy or parenteral hyper alimentation invasive candidial infections may also occur by non-*albicans*" species, such as *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis* and *Candida krusei*. Infact, *candida* genus represent the fourth most frequent pathogen isolated from the blood.

The most common species found in both sporadic and recurrent vulvovaginal candidiasis is *Candida albicans*, although in recent years there has been a growing number of infections with non-albicans species. *Candida lusitaniae* is an uncommon pathogen which produces fungemia most commonly some isolates of *candida lusitaniae* are resistant to amphotericin B (AmB) (Pappagianis *et al*., 1979; Hadfield *et al*., 1987; Blinkhorn *et al*., 1989). Osteomyelitis due to *candida* species is a rare example of such an invasion, which is the result of either hematogenous dissemination or direct traumatic inoculation. Such cases have been encountered in patients receiving some organ transplant (Jonnalagadda *et al*., 1996) or bone marrow transplant recipients (Ferra *et al*., 1994), intravenous drug addicts (Lafont *et al*., 1994), or the patients with a severely advanced disease having multi organ failure (Lew and Waldvogel, 1997; Gathe *et al*., 1987; Tang C, 1993).

Fluconazole, α-(2.4-diflurofenil)-α-(1H-triazol-1-methyl)-1H-1, 2, 4-triazol-1-ethanol, (FCZ) is an antifungal of belonging to triazole class. It is active against multiple species of *Candida* sp and is indicated in fungal diseases of oropharyngeal tract, esophagus, vaginal tract, and deep systemic infections. It acts by selective inhibition of ergo

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sterol, a steroid exclusive of the cell membrane of fungal cells. This disruption of ergo sterol is a cause of functional and structural changes in mycotic cell membrane and makes it prone to osmotic as well as immune mediated damage and decreases the cell adherence. Inhibition of cytochrome oxidative and per oxidative enzymes by azole derivative also increases the intracellular concentrations of peroxidases, which ultimately results in fungal cell death. Fluconazole is one of the most widespread used antifungal agents. its excellent pharmacokinetics, spectrum of activity, bioavailability, low toxicity and lack of interaction with other drugs, are few of the reasons for which fluconazole has so far been used to treat millions of people in the world fluconazole has a significantly better clinical and mycological cure rate compared with itraconazole in oropharyngeal candidiasis (Oude *et al*., 2004). Absorption by the gastrointestinal tract is high, and it spreads easily by body fluids. Oral suspensions of fluconazole are used widely in oral pseudo membranous candidiasis, because of its good adhesion to the surface of the oral mucosa and a rapid symptomatic response (Goins *et al*., 2002; Epstein *et al*., 2002; Lefebvre *et al*., 2002; Sholapurkar *et al*., 2009; Taillandier *et al*., 2000). Its efficacy has also been demonstrated in immune compromised patients, such as those HIV-infected, or with a neoplastic condition (Oude *et al*., 2004; Lyon and de Resende, 2006; Koks *et al*., 2002). Fluconazole also exhibits the activity against *C. lusitaniae.* patients suffering from candidial osteomyelitis who are unable to start or complete the required course of amphotericin B, fluconazole is a reasonable alternative and has been successful in its treatment (Tang, 1993; Meberg *et al*., 1997).

However, with time, a variety of resistance mechanisms, including over expression of various genes by the fungus, has been observed this problem has been attempted to be solved by the discovery of new drugs or modifications of existing ones. A growing interest in metal ion complexes as antimicrobial, diagnostic or chemotherapeutic agents has given rise to the wider application of inorganic medicinal compounds. This paper is also aimed at exploring antifungal activities of copper and nickel compounds of fluconazole to find the solution of emerging problem of drug resistant species. Furthermore to study the physical parameters of the newly synthesized complexes and structure elucidation was carried out thoroughly of each complex using the modern and sophisticated techniques like proton NMR, FTIR etc. The morphology of the fluconazole was compared with its complexes, changes were found in the morphology in the complexes in the respective micrographs.

## MATERIALS AND METHODS

### *Materials*

Reference samples of fluconazole (FCZ) was gift from Nabi Qasim Pharma (Pvt.) Ltd., Karachi. The copper, iron, manganese, cadmium, cobalt and nickel used in the form of hydrated chlorides, methanol of analytical grade and procured from Merck, Germany and freshly distilled water used as solvent.

### *Synthesis of the complexes*

An alcoholic solution of 0.1 M FCZ and 0.1M solution of each metal salt was prepared. 20.0ml of alcoholic solution of FCZ was taken in round bottom and 10.0ml of metal salt was transferred in the same flask. The mixture was refluxed for 3 to 4 hours on a water bath at 80°C and stirred time to time. The solid complexes were formed visible at the bottom of the flask. The mixture was cooled and filtered using what mann filter paper then precipitate was washed with hot methanol and dried at 60°C in an oven. The same synthetic procedure as that above was used except that the metal salt was replaced for the synthesis of the corresponding complex. Colored complexes were obtained except cadmium and manganese. The colors of each complexes are listed in table A.

### *Instrumentation and physical measurements*

Elemental analyses (CHN) were carried out on a Perkin Elmer 2400 Series II. The IR spectra were recorded in KBr pellets with a Shimadzu Prestige-21 spectrophotometer in the 4000-400cm$^{-1}$ range. The $^{1}$H NMR spectra of pure drug and its complexes were run in DMSO-d6 on an Avance AV-400, MHz spectrometer using TMS as an internal standard. Metals were analyzed by AA spectrophotometer PerkinElmer Analyst 700. SEM images were taken by Scanning Electron Microscope, JEOL JAPAN model no. JSM6380A with auto-coater JEOL JAPAN model no. JFC1500. Conductance and pH of 0.1% solution of complexes were measured in water by conductivity meter Janway 4071 and Metller Toledo MP220 pH meter, melting points of FCZ and its metal complexes were carried out by Stuart SMP3 melting point apparatus table A.

### *In vitro antifungal activity*

Fluconazole and its six corresponding complexes were evaluated *in vitro* for their antifungal activity by using two fungi namely *Candida albicans* and *Aspergillus niger* by the metod reported (Nisar *et al*., 2011). Antibiotic, Nystatin, AgNPsNystatin and AgNPs were dissolved in sterilized distilled water (24mg/ml). The sterilized Sabouraud's Dextrose agar medium was placed in a test tube and inoculated with the sample solution using three concentrations of 200µg/ml, 300µg/ml and 400µg/ml. The test tubes were kept in slanting position at room temperature for overnight. The fungal cultures of both species under study were then inoculated onto the slant. The samples were incubated for seven days at 29°C. After completion of duration these tubes were taken out and percentage growth inhibition was calculated with reference to the negative control by applying the formula below:

**Table A**: Physical properties of FCZ and its metal complexes

| Compound | Color | M.P (C) | pH 0.5% | Cond. (mS) 0.5% |
|---|---|---|---|---|
| Fluconazole (FCZ) | White | 138±3 | - | - |
| Mn- FCZ | White | 245 D±3 | 5.95 | 0.37 |
| Cu-FCZ | Sky blue | 190 D±3 | 4.07 | 0.30 |
| Co-FCZ | Purple | 270 D±3 | 6.09 | 0.35 |
| Fe-FCZ | Yellowish Golden | 220 D±3 | 2.61 | 0.10 |
| Cd-FCZ | White | 225 D±3 | 6.07 | 0.31 |
| Ni-FCZ | Sky Blue | 270 D±3 | 6.07 | 0.28 |

depicted in Table B.

**Table B**: Comparison of percent elemental composition in metal complexes

| Compound | % C | % H | % N | %Metal |
|---|---|---|---|---|
| | Theoretical/Practical | Theoretical/Practical | Theoretical/Practical | Theoretical/ Practical |
| [a][Mn(FCZ)$_2$Cl$_2$].2H$_2$O | 40.31/40.66 | 3.61/3.57 | 21.70/21.86 | 7.09/6.95 |
| [b][Cu (FCZ)$_2$Cl$_2$].6H$_2$O | 36.48/36.23 | 4.21/4.01 | 19.64/19.34 | 7.43/7.46 |
| [c][Co (FCZ)$_2$Cl$_2$].H$_2$O | 41.05/40.87 | 3.42/3.41 | 22.10/22.19 | 7.75/7.48 |
| [d][Fe(II)(FCZ)$_2$Cl$_2$].3H$_2$O | 39.34/39.46 | 3.78/3.79 | 21.18/20.72 | 7.04/7.10 |
| [e][Cd(FCZ)$_2$Cl$_2$].H$_2$O | 38.32/38.27 | 3.19/2.97 | 20.63/20.54 | 13.80/13.17 |
| [f][Ni(FCZ)$_2$Cl$_2$].4H$_2$O | 38.32/38.68 | 3.93/3.91 | 20.63/20.45 | 7.21/7.19 |

M. Wt. = [a]774.47g/mole, [b]855.08g/mole, [c]760.47g/mole, [d]793.38g/mole, [e]813.94 g/mole and [f]814.16g/ mole

$$\% \text{ inhibition of fungal growth} = \frac{100 \text{ linear growth and test (mm)}}{\text{Linear growth in control (mm)}} \times 100$$

Miconazole and amphotericin B were used as standard drugs, while miconazole, amphotericin B and DMSO were used as positive and negative controls as reported (Nisar *et al*., 2011)

***Physiochemical studies***

Metal complexes of FCZ were decomposed at 190 to 270°C, which were higher than the melting points of the pure FCZ, which show formation of new compounds. Solubility of complexes were checked in different solvents. All complexes were dissolved in polar solvents, which is indicate that complexes are polar in nature. Complexes have almost neutral coordination sphere with almost neutral pH table A.

***CHN and metal analysis***

The quantitative determination of carbon, hydrogen and nitrogen in each complex was determined by elemental analyzer while the percentage composition of metal was calculated on atomic absorption. The results obtained are in agreement with the theoretical calculated values. The metal to ligand ratio found to be 1:2 in all complexes depicted in table B.

***IR spectra***

All FCZ complexes exhibit the characteristic peaks of parent molecule in the range of 1110-1620cm$^{-1}$. Due to the different metal ions in the six complexes, the distinctiveness peaks of fluconazole are migrated from their region to some extent e.g. FCZ ring stretching occurred at 1423cm$^{-1}$ significantly decreased in the metal complexes. Similarly, vibrational frequency of ring breathing observed at 1140cm$^{-1}$ has been shifted to lower frequency rang 1124cm$^{-1}$ in the complex. A little bit shifting from 1082cm$^{-1}$ to 087cm$^{-1}$ of C-OH peak of FCZ in metal complexes indicates that hydrogen of O-H has not dissociated during complexation/coordination Thus suggested the binding mode and it attributed that binding side in all complexes may be nitrogen of triazole IR peaks are summarize in table C.

***UV Visible spectra***

UV scan of FCZ in distilled water showed one peak at 260nm with shoulder at 265 nm they are may be due to $\pi$ to $\pi^*$ transition, in metal complexes except iron (II) and Cu(II) no significant changed were observed, in Fe (II) complex with FCZ three bands appeared at 240, 310 and 360 nm, 240nm peak may be due to FCZ peak which shifted to lower $\lambda$ of 20nm, whereas remaining two transitions are may be due to $^1A_{1g}$ to $^1T_{1g}$ and $^1A_{1g}$ to $^1T_{2g}$. In Cu (II) one more peak appeared at 328 nm with ligand peak which was not appeared in free ligand and free metal spectra this peak may be due to back bonding between metal to ligand.

***1H-NMR spectra***

All peaks of complexes are more or less comparable with each other and comparable with the FCZ molecule. However, shapes of the peaks are not as sharp as peaks of FCZ but the integration of each peak does match with the integration of FCZ peaks. The integration of each peak in the spectra of complexes clearly indicates the same number proton as reported for the FCZ. The regions of peaks and their pattern of splitting in the spectra of

complexes are same region as in FCZ spectra. The $^1$H-NMR spectra of complexes exhibits two singlets at δ 8.2 and 7.6 assigned for two protons of triazole ring, three multiplets near δ 7.1 to 6.8 allocated for the three aromatic protons of the m-diflurophenyl ring of FCZ while two doublets at δ 4.9 and 4.6 due to two sets of methylene protons of FCZ. These observations are in consistent with the structure proposed for the metal complexes of FCZ under investigation fig. 1.

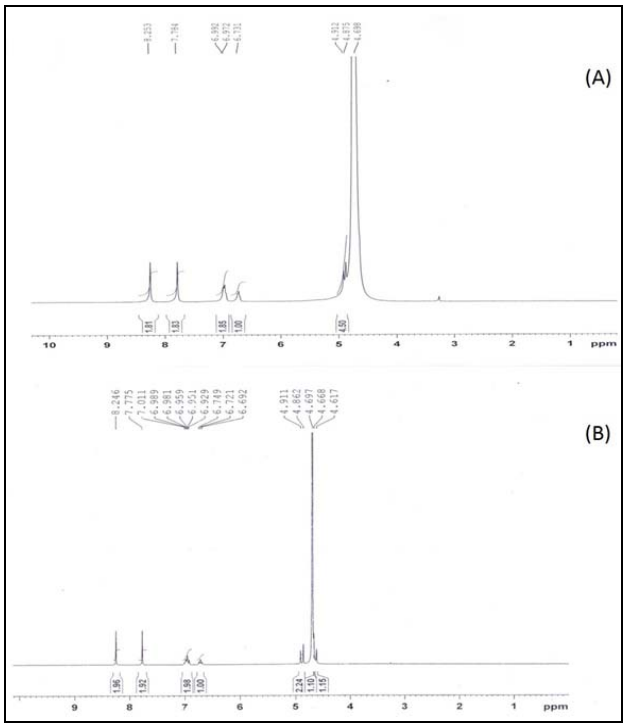


**Fig. 1**:$^1$H-NMR spectra of (A) pure drug FCZ and (B) Cd-FCZ complex

***Morphological studies***

To explore the possible morphological changes caused by complex formation, scanning electron microscopy (SEM) studies were performed on pure flucanazole and its metal complexes. This technique is considered to be a powerful tool to explore the surface morphologies and particle size distributions of a wide range of materials. Although SEM does not completely confirm complex formation, it can help us identifying the existence of a single phase hinting towards a possible complex formation.

For the pristine fluconazole and its metal complexes, the resulting micrographs are presented in fig. 2(a-f). Pure fluconazole is a white crystalline solid occur in different polymorphic forms (Park *et al*., 2007; Kastelic *et al*., 2010). The micrograph of the pure fluconazole lig and used in this study is presented in fig. 1a which reveals a flaky-slab like morphology with a rock-like appearance. The surface of the particles is smooth indicating a homogeneous phase of the ligand. Similar morphology for fluconazole was also reported earlier (Desai and Dharwadkar, 2009; Park *et al*., 2007; Marciniec *et al*., 2007) by others.

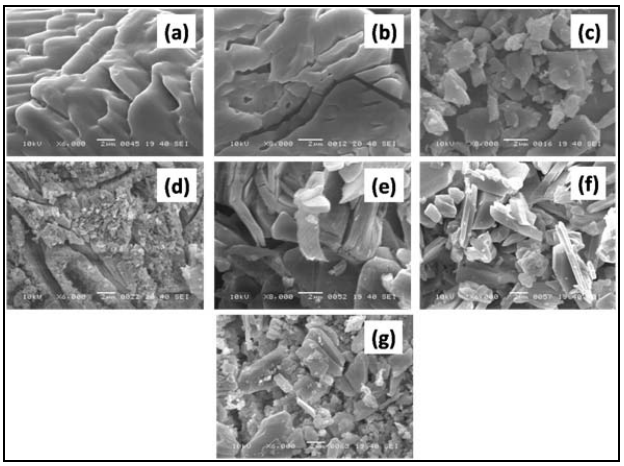


**Fig. 2**: SEM Micrographs of (a) FCZ (b) Co-FCZ (c) Mn -FCZ (d) Fe-FCZ (e) Ni-FCZ (f) Cu-FCZ and (g) Cd-FCZ Complexes

The SEM micrographs did not reveal any marked changes in the crystalline structure of fluconazole-Co complex as a similar rock-like appearance in evident (fig. 2b). The image is featureless apart from cracks in the crystals which may also be attributed to the artifacts arising due to drying during the sample preparation procedures for SEM. These facts made the interpretation a bit complicated and it is hard to designate the particle sizes due to the homogeneous solid smooth surface. Similar to what was observed for pure fluconazole, fluconazole-Co complex also exhibit a uniform matrix, which leads us to believe that we are dealing with homogeneous phase material (Khan *et al*., 2013). This suggests the presence of a single component in the complexes indicating a complete complex formation with the drug uniformly dispersed at the molecular level (Malik and Wankhede, 2015).

Fig. 2c shows the morphology of the fluconazole-Mn complex where the presence of well-defined crystals free from any shadow of the metal ions on their external surface is evident. The morphology appeared as large and small rock-like crystalline particles of rather irregular shapes and a broad size distribution. Compared to what was observed for the pristine fluconazole particles (fig. 2a), the fluconazole-Mn complex exhibits a marked reduction in the particle sizes. Few small particles in nanometer range are also visible which have a tendency to agglomerate formation. The complex also exhibits a homogeneous matrix suggesting a complete complex formation and a uniform distribution of drug at the molecular level (Malik and Wankhede, 2015).

Fig. 1d shows the morphology of the fluconazole-Fe complex. Compared to the pure fluconazole (fig. 2a), a marked change in the morphological features is clearly

**Table C**: FTIR data of pure FCZ and Metal complexes of FCZ

| | O-H | C-H str, triazole | C-H str, arom ring | C=C str, arom ring | Triazole ring str. | O-H deform | CH arom. Ring in plane deform | CH Triazole ring in plane deform. | Triazole ring breathing | C-OH str. | Triazole ring deform | Arom. ring deform |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FCZ | 3180 | 3111 | 3062 | 1620<br>1512 | *1423 | 1276 | 1247 | 1213 966 | 1140 | 1082 | 914<br>651 | 677 615<br>528 |
| Cu - FCZ | - | 3132 | 3049 | 1612<br>1525 | 1502<br>1421** | 1278** | - | 1207 966** | 1124 | 1087 | 912<br>646 | 673 619<br>524 |
| Ni - FCZ | - | - | - | 1616<br>1525 | 1502<br>1423** | 1278** | - | 1205 966** | 1124 | 1087 | 910<br>650 | 677 522 |
| Cd - FCZ | - | 3122 | - | 1618<br>1525 | 1504<br>1423** | 1278 | 1247 | 1217 966** | 1130 | 1095 | 896<br>655 | 677 528 |
| Co - FCZ | Band | Band | Band | 1618<br>1523 | 1500<br>1423** | 1276 | - | 1203 968** | 1124 | 1087 | 912<br>650 | 677 524 |
| Fe - FCZ | - | Band | Band | 1618<br>1522 | 1502<br>1419** | 1276 | - | 1201 968** | 1124 | 1087 | 914<br>651 | 677 524 |

* One Triazole ring stretching peak 1507 is merge in 1512 peak of C=C stretching, aromatic ring
** Peak intensity decreased from FCZ peak

visible as the surfaces of the particles are considerably coarse. Interestingly, small crystals with the size ranges in nanometers can be seen distributed throughout the surface. These finding suggest that the complex is likely to be polycrystalline in nature (Joseph and Janaki, 2014).

Presence of a well-defined crystalline morphology is evident in the SEM micrographs of fluconazole-Ni complex presented in fig. 2e. Compared to the pure fluconazole (fig. 3a), a change in some morphological features in the form of reduction in the particle diameters and the edge thickness is visible. The crystals of fluconazole -Ni complex exhibit non-spherical, platelet-shaped irregular particles of rather broad size distribution. The surface of the particles is free from any shadow of the metal ions, which generally give a sharp contrast in electron microscopy imaging. A complete complex formation and a uniform distribution of drug at the molecular level can be inferred from the homogeneous matrix of the particles (MalikAnd Wankhede, 2015).

Fig. 1f depicts the SEM micrographs of fluconazole -Cu complex. Similar to the fluconazole -Ni complex particles (fig. 2e), the crystals of fluconazole -Cu complex also exhibit non-spherical, platelet-shaped morphology comprising of particles with a somewhat broad size distribution. The edge thickness and the particle diameters are smaller probably due to the differences in the coordination properties of the two metals involved in the complexation (Cu and Ni). Similar to the pristine fluconazole particles (fig. 2a), fluconazole-Cu complex also exhibits a single phase homogeneous matrix indicating towards successful complexation (Malik and Wankhede, 2015).

The SEM micrograph for fluconazole-Cd complex particles revealed a non-spherical, platelet-shaped morphology comprising of irregular shaped particles (fig. 2g). The particle size distribution appeared to be quite broad. Small crystals with the size ranges in nanometers can also be seen distributed throughout the surface. Uniform matrix of the synthesized complex leads us to believe that the material is in homogeneous phase and the complex formation was successful (Malik and Wankhede, 2015).

***In vitro antifungal activity***

Fluconazole a fungal drug widely used to treat multiple infections of Candida species, particularly to deals to treat vagina, mouth, throat, and bloodstream candidiasis. In present study fluconazole and its synthesized six metal complexes were tested against two species of fungus, Aspergillus Niger ATCC 16404 and Candida albicans ATCC 10231.The minimum inhibitory concentration (MIC) of newly synthesized complexes was determined by assaying at 400µg/mlConcentration. The FCZ was also assayed at the same concentration used as reference. The assay results of antifungal activity are systematized in table D.

The antifungal activity against two fungal species named *Aspergillus niger* and *Candida albican* showed that ligand FCZ and it corresponding complexes were devoid of antifungal activity against *Aspergillus niger*. However,

**Table D**: Anti-fungal activity of FCZ and metal complexes

| Concentrations of compound 400µg/ml | *Aspergillus Niger ATCC 16404* | *Candida albicans ATCC 10231* |
|---|---|---|
| | % Inhibition | % Inhibition |
| Fluconazole | 0 | 65% |
| Mn-FCZ | 0 | 5% |
| Cu-FCZ | 0 | 10% |
| Co-FCZ | 0 | 5% |
| Fe-FCZ | 0 | 2% |
| Cd-FCZ | 0 | 20% |
| Ni-FCZ | 0 | 2% |

FCZ showed activity against albicans but none of the complexes was proved more potent than its parent compound. FCZ exhibit 65% inhibition of candida albicans at MIC of 400ug/ml. whereas Cd- FCZ and Cu-FCZ had 20% and 10% inhibition respectively. On the other hand Co-FCZ and Mn-FCZ compounds expressed equal inhibition of 5% only. The remaining of the two complexes namely Ni-FCZ and Fe-FCZ had negligible antifungal activity.

## DISCUSSION

Candida is the normal flora of GIT and is found in about 65-76% of healthy human population but at the same time both superficial as well as deep seated infections including oral and vulvovaginal candidiasis can also be caused by the some specie once the immunity is compromised.

Fluconazole (2,2,4-diflurophenyl)-1,3-bis (1H-1,24-triazole-1-yl) propane-2-ol is the most popular and widely used antifungal agent globally. A large part of world population is treated with FCZ for fungal infection so far. This triggered us towards the synthesis of derivatives of metal complexes of FCZ and explore them for their biological activity against candida species. But due to the limitation of availability of various species in the microbial laboratory only single specie was taken to test against the newly prepared FCZ complexes. Some other fungal species were also reported in the literature to possess activity against FCZ derivatives. Hence the antifungal activity was performed against two species of fungi, *Aspergillus niger* and *Candida albican*. All complexes were tested against *Aspergillus niger* but all were proved inactive nevertheless four complexes demonstrated activity to some extent against *Candida albican*.

The structure of synthesized complexes was established by using physical methods and instrumental techniques. The physical properties including visual tests, solubility, melting point, etc. were determined. The molecular formula of complexes were calculated theoretically and confirmed by elemental analysis and atomic absorption. The results revealed that the theoretical values were in agreement to theoretically calculated formulas. The UV and IR values were also found in accordance to expected values but some peaks showed migration or shifting upon comparison with the spectra of FCZ thus indicating the transformation of FCZ into its corresponding complex. In the spectra of H-NMR the integration of all protons of each complex was established exactly the same as proposed in molecular formula table B. However, the slight shifting of peaks and also splitting pattern of peaks were observed in proton spectrum, which is again in accordance to the behaviour reported in the literature.

Morphologies of pure flucanazole and its metal complexes were probed by scanning electron microscopy (SEM) which revealed noticeable changes in some morphological features, such as particle shapes and size distributions, after complexation. Remarkably, the complexes exhibit single-phase homogeneous morphology free from metal particles which lead to the conclusion that the material is likely in homogeneous phase and the complex formation was successful

## CONCLUSION

In the last few decades the interest in metal ions complexes have been grown enormously as chemotherapeutic agents. Thus the aim of this study was to prepare metal (II) complexes of FCZ, characterize and evaluate their biological activities against *Aspergillus niger* and *Candida albican*. This piece of work certainly contribute in the field of coordination chemistry and attract the researchers to conduct more research in future to uncover other findings, parameters and studies like single crystal formation, FT-NIR, Raman etc. on these complexes and also prepare more complexes using different metal salts while keeping the same starting material FCZ. Based on the biological studies further research is also recommended involving more number of candidal species for testing the biological activity of complexes.

The present works triggered us and also invites more attention of scientific community towards the evaluation of these metal complexes of fluconazole and further preparation of different derivatives of fluconazole in order

to investigate against other biological activities like anti-cancer, anti-platelet, anti-microbial etc.

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