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International Journal of Pharmaceutics 289 (2005) 179–187
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Physicochemical studies on Ciclopirox olamine complexes with divalent metal ions

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Received 21 February 2004; received in revised form 11 November 2004; accepted 11 November 2004

Abstract

Ciclopirox olamine (CPO) metal complexes have been prepared and characterized using elemental analysis, infra red (IR), melting point and differential scanning calorimetry (DSC). Spectroscopic titration using molar ratio method indicated the occurrence of 1:1 complexes for CPO with almost all the examined metals. Physicochemical properties were also studied including aqueous solubility and apparent partition coefficient. Results showed that generally complex formation dramatically decreased the solubility and increased apparent partition coefficient. However, some metal complexes exhibited opposite effect. It could be concluded that complex formation can modify the solubility and apparent partition coefficient, which may suggest the use of complexes to manipulate the physicochemical properties of the drug.

Keywords: Ciclopirox olamine; Metal ion complexes; Partition coefficient

1. Introduction

Ciclopirox olamine (CPO) is a hydroxy-pyridone anti-mycotic drug known chemically as 6-cyclohexyl-l-hydroxy-4-methylpyridin-2-(lH)-one (Fig. 1). It is available commercially as a 1% aqueous topical cream preparation (Batrafen®) intended for skin and nail fungal infections (Fredriksson and Savopoulos, 1981; Jue et al., 1985). The drug is usually available as its ethanolamine. Pharmacological studies on animals have shown that the compound is not expected to produce serious toxicological systemic effects at the doses used in local therapy (Alpermann and Schutz, 1981). The same study on laboratory animals also revealed favorable therapeutic index with no prohibitive mutagenicity or carcinogenicity (Alpermann and Schutz, 1981).

The drug is also available as 8% nail lacquer for the treatment of fungal infections of nails (Ceschin-Roques et al., 1991; Bohn and Kraemer, 2000a,b; Gupta et al., 2000). This pharmaceutical dosage form has been shown to provide high-concentration gradient that

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doi:10.1016/j.ijpharm.2004.11.009

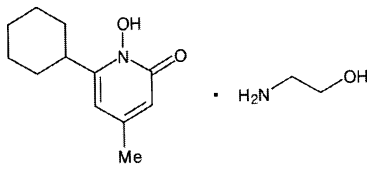

Fig. 1. Ciclopirox olamine.

enables the penetration of the antifungal drug into nail structure (Bohn and Kraemer, 2000a). CPO has been shown to possess antimicrobial activity against a broad range of microorganisms including *Candida* spp. (Gupta et al., 2000), *Trichophyton* spp. (Sehgal, 1976), dermatophytes and non-dermatophytes (Jue et al., 1985), yeast and even Gram-negative and -positive bacteria including strains that are resistant to penicillins (Bohn and Kraemer, 2000a). It has been shown that 1.3% of the applied topical cream can be absorbed percutaneously, and slightly higher percentages could be absorbed through the surface of the finger nails (Kellner et al., 1981). The horny layer of cadaverous skin was found to contain the highest concentration of the drug. CPO was found to penetrate the skin via the epidermis and hair follicles.

Perhaps the most common clinical use of CPO is for the treatment of onchomycoses, which is a fungal infection that affects the nail tissue and is usually difficult to eradicate (Gupta et al., 2003). Long courses of treatment are usually required to get rid of the infection, partly because of suboptimal penetrability of the used antifungal agents into nail structure. Clinical trials have shown that CPO was effective in treating onchomycoses (Bohn and Kraemer, 2000a; Gupta et al., 2000).

The mechanism of action of CPO has been the objective of few interesting studies (Iwata and Yamaguchi, 1981; Niewerth et al., 2002; Leem et al., 2003; Niewerth et al., 2003). Some reports have hinted that the drug works by binding to ferric ions, and thus, depriving the fungus from such essential metal ions (Iwata and Yamaguchi, 1981; Niewerth et al., 2002). The intracellular depletion of essential ions was believed to be brought about through blockage of their uptake from the medium (Iwata and Yamaguchi, 1981). Others have implied that the drug acts through binding to multiple essential proteins that participate in various components of cellular metabolism, including DNA replication, DNA repair and cellular transport (Leem et al., 2003).

Recently, CPO has been shown to be effective inhibitor for the enzymes deoxyhypusine hydroxylase and prolyl 4-hydroxylase (Clement et al., 2002), which suggested new potential application for CPO in the treatment of solid tumors. Dependence of CPO action on limitation of iron was also suggested by one study by using gene expression techniques (Niewerth et al., 2003).

Many drugs are capable of forming chelate complexes with metal ions with tetracycline representing a classical well-known example. In recent years, there has been an increasing interest in this area (Wang, 1998; Richardson, 2002; Finefork et al., 2003; Levenson, 2003; Pierre et al., 2003; Pradines et al., 2003). Drug–metal complexes have also been shown to modify the pharmacological activity of the parent drug (Matsukara and Tanaka, 2000; Sharma et al., 2003) or they might be involved in the mechanism of action of the drugs (Wang, 1998; Buss et al., 2003; Levenson, 2003). Drug–metal complexes have also been shown to modify the pharmaceutical properties of the drugs; for example the absorption of quinolone antibiotics was significantly decreased by binding to metal ions (Lomaestro and Bailie, 1991).

In this work, a study of the potential interaction between CPO and divalent metal ions is presented. Complexes were prepared, characterized and the potential effect of complexes on solubility and partition coefficient was examined.

2. Materials and methods

CPO was purchased from Sigma (Sigma–Aldrich Co., St. Louis, USA). Ethanol, *n*-butanol and methanol were from GCC laboratory reagent (Hampshire, UK), *n*-octanol was from Riedel-dettaën (GmbH, Germany) and Tris–buffer (ultra-pure) was from ICN Biomedicals (Hampshire, UK).

$CaCl_2$ and $CuBr_2$ were from Fluka-Garantie für (Buchs-Switzerland). $MgSO_4{\cdot}7H2O$ and $ZnSO_4{\cdot}7H_2O$ were from Merck (Darmstadt, Germany). $FeSO_4{\cdot}7H_2O$ was from Loba Chemie Ltd. (Bombay, India). $MnSO_4{\cdot}H_2O$ was from Dr. Paul Lohmann® (GmbH, Germany).

All UV measurements were made using a 1 cm quartz cell and Cary Varian spectrophotometer. Infra red (IR) spectra were recorded on an Infinity Gold FT-IR, Mattson®. Differential scanning calorimetry (DSC) isotherms were recorded using TA 4000, Mettler® DSC system. Melting points were measured using the melting point apparatus SMP1, Stuart scientific®. Elemental analysis was carried out using Eurovector elemental analyzer (EA3000, Milan, Italy).

2.1. Procedure

2.1.1. Preparation and characterization of the CPO metal complexes

Complexes were prepared in Tris–buffer pH 7.0 by mixing equimolar amounts of the metal and the complex. After 6 h standing at room temperature (~22 °C), the obtained complexes were filtered and dried in a desiccator filled with silica. Melting points were obtained for complexes using the capillary method. Complexes were subjected to standard elemental analysis using Eurovector elemental analyzer. IR spectra were obtained for the dried complexes using KBr disk method. DSC scans were obtained for the solid complexes in the range 25–350 °C with a heating rate of 10 °C/min.

2.1.2. Spectroscopic titration of CPO with metals in Tris–buffer (pH 7.0, octanol)

A stock solution of CPO (0.5 mM) was prepared in 5 mM Tris–buffer pH 7.0. Stock solutions of each of the metals to be studied were also prepared in Tris–buffer at molar concentration of 1.0 mM. For each titration experiment, 1.5 ml of the drug stock solution was added to each of 12 test tubes, and calculated volumes of the metal stock solution to be studied were added to the test tubes volumetrically so that the desired drug-to-metal ratio (r) is obtained. In 12 test tubes, r-values in the range 0.125–4 were prepared. Total volumes were completed to 10 ml with Tris–buffer pH 7.0. Solutions were mixed well and left to stand for 15–30 min. UV spectra were obtained for all solutions that did not show turbidity or precipitate upon addition of the metals in the range 200–350 nm. Tris–buffer (5 mM) was used as a blank and the absorbance was measured at appropriate wavelengths.

Some metal complexes appeared to have low water solubility as turbidity, or precipitates appeared immediately after mixing metal with the drug solution. For such metal complexes (Cu^{2+}, Fe^{2+}, Mn^{2+} and Zn^{2+}), 10 ml of octanol was added to the test tubes. Test tubes were shaken and left to equilibrate over night and spectra recorded for the clear octanol layer the next day in the range 200–350 nm, and absorbance was measured at desired wavelengths (227, 303 and 322 nm). The octanol layer was removed and the spectrum was recorded for the remaining aqueous portion as well.

2.1.3. Determination of the solubility of CPO and its metal complexes in 5 mM Tris–buffer pH 7.0

Two and a half milligrams of the drug was added to 5 ml of 5 mM Tris–buffer (pH 7.0). Test tubes were then placed on a shaker at R.T. for 72 h. Test tubes were then centrifuged for 10 min at 4500 rpm, filtered, diluted and absorbance measured at wavelength of 322 nm. Concentrations of soluble CPO were estimated using a calibration curve obtained at the same time of measurement. A representative regression equation for CPO alone at 322 nm could be given by $Y = 9.4825X - 0.0833$, ($R^2 = 0.995$). The relationship was linear in the absorbance range 0.089–1.38.

Super-saturated solutions of the complexes at a drug-to-metal ratio of 1:1 ($r = 1$) were prepared in order to determine their solubility. Stoichiometric analyses have shown that CPO metal complexes occur as 1:1; therefore, the required amount of the complex was prepared directly in solution by mixing the appropriate volumes of each of the metal and drug solutions together. For the complexes of CPO with Mn, Zn, Cu and Fe, 2 ml of CPO solution (0.135 mg/ml) + 1 ml of 1 mM metal solution in buffer were mixed. For the complexes of CPO with Mg^{2+} and Ca^{2+}, 2 ml of CPO solution (1.35 mg/ml) + 1 ml of 0.01 M metal solution in buffer were mixed. Test tubes (three sets) were placed on a shaker for 72 h, and then centrifuged at 5000 rpm for 15 min.

Because the absorbance values of the supernatants were too low for accurate measurements (<0.01), the precipitated amount was determined. The amount of the dissolved complex was estimated by the difference between total concentration of the complex and the precipitate. The filter paper with the precipitate was placed in a test tube and 10 ml ethanol was added to each test tube so that complete dissolution of the complexes was ensured.

Because all complexes exhibited isospestic point at 322 nm, a calibration curve was constructed at 322 nm using CPO in ethanol and the same equation was used for calculating the concentration of the various complexes except for iron complexes. Iron complexes appeared to have isospestic point at 292 nm, which was the wavelength used to obtain the calibration curve for determining the concentrations of CPO–Fe complexes. Linear relationship could be obtained at 322 nm over the absorbance range 0.148–1.05 and represented by $Y = 10.777X + 0.0227$ ($R^2 = 0.9854$). For iron complexes, the relationship was linear over the absorbance range 0.312–1.2 and the equation could be described by $Y = 24.241X - 0.0091$ ($R^2 = 0.9935$).

2.1.4. Determination of the apparent partition coefficient of CPO and its metal complexes

Aliquot (2 ml) of 0.48 mg/ml CPO solution in 5 mM Tris–buffer was transferred volumetrically to each of three test tubes and 2 ml of *n*-octanol was then added. Test tubes were placed on a shaker for 24 h at room temperature and then centrifuged at 4500 rpm for 10 min. Half milliliters of the octanol layer was diluted to 2.5 ml with *n*-octanol and absorbance measured at 322 nm. The concentration of CPO in the octanol layer was determined according to calibration curves of the drug in octanol at 322 nm obtained at time of measurement. A linear relationship was obtained for the drug in octanol over the absorbance range 0.198–1.3 that could be described in the following equation: $Y = 10.539X + 0.0362$ ($R^2 = 0.9964$). The concentration of CPO in the aqueous phase was estimated by difference and consequently, the partition coefficient was calculated.

For CPO–metal complexes, 1 ml of the drug solution (5 mM) in Tris–buffer was mixed in test tubes with 0.5 ml of the metal solutions (1 mM) in Tris–buffer ($r = 1$). One and a half milliliters of octanol was added and test tubes were put on the shaker for 24 h at room temperature. Then the test tubes were centrifuged at 4500 rpm for 10 min and the absorbance of the octanol portion was measured at 322 nm for all the complexes except CPO–Fe complex, which was measured at 292 nm. The apparent partition coefficients were calculated in the same manner as for the drug but in these sets, the initial amount of complex is presumed to be equal to the amount of drug added to form the 1:1 complexes.

3. Results and discussion

3.1. Preparation and characterization of complexes

Complexes were prepared as described in the experimental section in Tris–buffer at $r = 1$. Evidence on complex formation was obtained from melting point, DSC, elemental analysis and IR spectroscopic techniques. Table 1 lists the measured melting points for CPO and its metal complexes. Data of Table 1 supported that new compounds (chelate complexes) have been formed with melting points significantly different from that of CPO for most of complexes. These results were also supported by DSC data.

Fig. 2 represents DSC curves for CPO and CPO–Cu^{2+} complex. The complex exhibited two exothermal peaks at about 315 and 340 °C while the drug had two endothermic peaks at about 100 and 150 °C. The endothermal peak for the drug at 100 °C was most likely due to water contained within CPO raw material (4.5%) as determined by Karl–Fisher titration. The appearance of two exothermal peaks for the complex could be attributed to oxidative degradation, which was also noticed during measurement of the melting points. The isotherm of the complex did not show any endothermic ∼145 °C characteristic of the free drug. Thus, DSC provided direct evidence that the dried precipitate was the complex form only, without carry over from the free drug.

IR spectra of CPO and two examples of the complexes (CPO–Ca^{2+} and CPO–Cu^{2+}) are shown in Fig. 3. Summary of the major bands in the spectra of CPO and its metal complexes is presented in Table 2. IR spectra of the complexes in general showed slight shift in principal peaks of CPO. The major stretching band in the

Table 1
Melting points of CPO and its metal complexes

Drug	Melting point (°C)	Notes
CPO	140–145	Without decomposition
CPO–Mg^{2+} complex	312–318	With decomposition
CPO–Ca^{2+} complex	313–318	With decomposition
CPO–Mn^{2+} complex	146–155	With decomposition
CPO–Fe^{2+} complex	142–145	With decomposition
CPO–Cu^{2+} complex	312–320	With decomposition
CPO–Zn^{2+} complex	125–131	Without decomposition

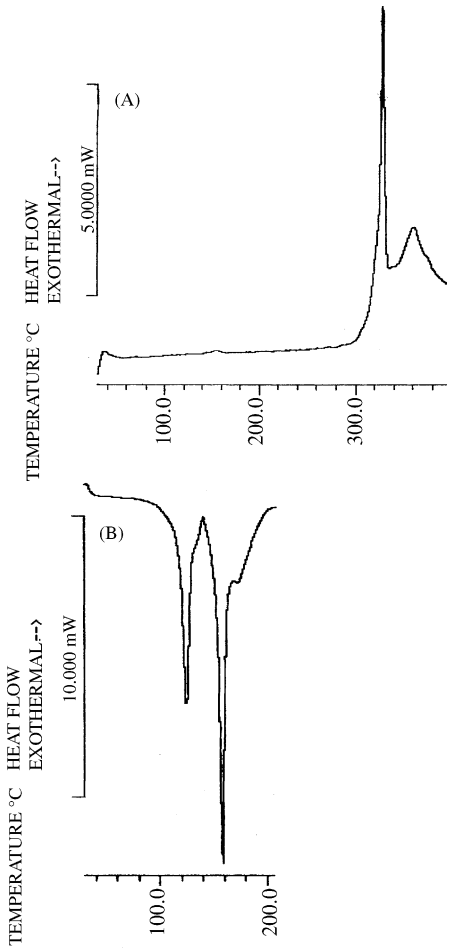

Fig. 2. Differential scanning calorimetry (DSC) scans of (A) CPO–Cu^{2+} complex and (B) CPO.

region of 3000–3500 cm^{-1} disappeared completely in the spectra of all complexes. This band corresponds to hydrogen bonding of associated water molecules (4.5%) and/or intramolecular hydrogen bonding between hydroxyl and carbonyl oxygen (3221 cm^{-1}). Thus, an indication of the possible involvement of the carbonyl group in complex formation was obtained. However, the major changes associated with the formation of complex were the characteristic of carbonyl stretching (1640–1548 cm^{-1}). Generally, all complexes showed a difference between the two stretching bands (within the carbonyl region) less than that of the free drug, which again indicates complex formation involving the carbonyl group (Bucci et al., 2000). Thus, additional evidence on complex formation was obtained from IR spectra.

Table 2
Summary of the major changes (carbonyl) of the infra red spectra of CPO–metal complexes as compared to CPO

Complex	Band l	Band 2	Band 3	Change (Δ) in carbonyl bands (cm^{-1})
CPO	1514	1548	1640	92
CPO–Mn^{2+}	1505	1550	1620	70
CPO–Mg^{2+}	1503	1551	1621	70
CPO–Ca^{2+}	1519	1552	1637	85
CPO–Cu^{2+}	1501	1522	1627	105
CPO–Fe^{2+}	1506	1550	1627	77
CPO–Zn^{2+}	1511	1551	1631	80

3.2. Spectroscopic titration of CPO with metals in Tris–buffer, pH 7.0

Complex formation was also studied in buffered aqueous solution using UV spectroscopy. Complex formation was evident by the appearance of precipitate (turbidity) as soon as metal solutions (with the exception of Ca^{+2} and Mg^{2+}) were added to CPO solutions. Consequently, direct UV spectroscopic titration of the complexation reaction was prohibited. Therefore, *n*-octanol was added to aqueous solutions and UV spectra were recorded for the octanol layer as well as for the remaining aqueous layer. Since no absorbance was detected for the aqueous layer at all *r*-values ($r = 0.12$–4) over the entire range of wavelengths, it was assumed that all of the drug or its complexes left the aqueous layer to the organic layer when partitioned between the two phases. Therefore, the obtained UV spectra in octanol for each metal (titration experiment) were assumed to represent those occurring in the aqueous buffer. For most of the studied complexes, UV spectra showed progressive shifts at certain wavelengths (222–230 nm) as metals were added to solutions of CPO up to certain ratios after which absorbance of solutions remained practically constant. An example is presented in Fig. 4, which shows overlaid UV spectra of solutions containing constant amount of CPO and increasing concentrations of the metal Mn^{2+}. These shifts were taken as evidence for complex formation. The classical molar ratio plots were obtained (Fig. 5) and used for estimating the stoichiometry of the complexation reaction (Brewer, 1980). The breaking points

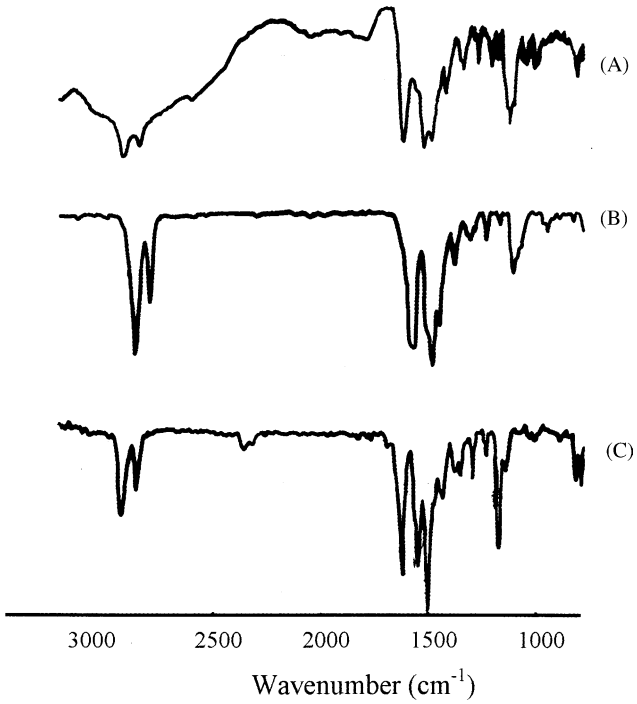

Fig. 3. Infra red (IR) spectra of (A) CPO, (B) CPO–Ca^{2+} complex and (C) CPO–Cu^{2+} complex.

in the molar ratio plots correspond to the stoichiometry of complexation reaction. Accordingly, plots of all complexes indicated (within the margin of experimental errors) a stoichiometry of 1:1. An exception was the titration of the drug with magnesium, where molar ratio plots showed no definite breakpoints, which may be due to lack of difference in the UV absorbivities of CPO and its Mg^{2+} complexes.

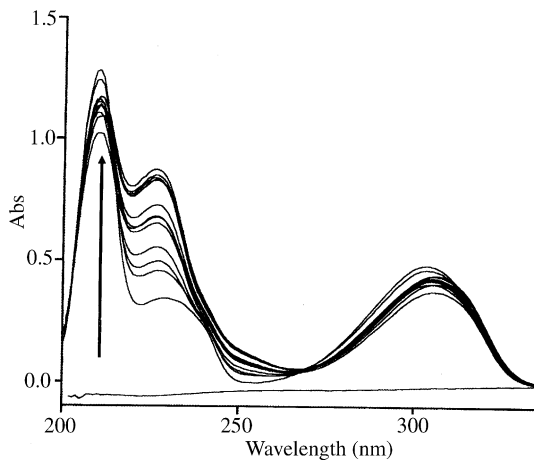

Fig. 4. Overlaid UV spectra of CPO solution titrated with Mn^{2+}. Arrow indicates the direction of increasing metal concentration.

In order to eliminate the possibility that the observed spectral shifts within the region studied has resulted from the added free metal to solutions of CPO, solutions containing the appropriate amounts of the metal with no CPO were treated and measured in the same way. In octanol, all the metals behaved in the same manner where no absorbance was detected over the entire absorbance range. In buffer, however, Cu^{2+} exhibited significant absorbance in the region 200–300 nm.

In order to ensure that all of the drug and/or its metal complexes were transferred to the octanol layer, UV spectra were recorded for the remaining aqueous buffer after removal of the organic layer. In all cases, no absorbance was detected in the entire UV range examined except for Cu^{2+} complexes, which was due to intrinsic absorption of the excess free-Cu^{2+} remaining in the aqueous phase. Therefore, it was acceptable to assume that almost all of the free drug or its metal complexes left the aqueous layer to the organic phase upon partitioning. It was interesting to note that solutions

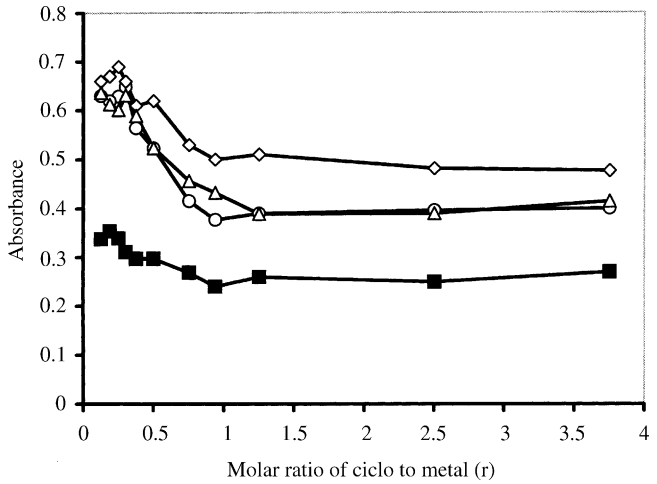

Fig. 5. Molar ratio plots of CPO titrated with Mn^{2+} (◊), Zn^{2+} (△), Ca^{2+} (◯) and Fe^{2+} (■). Measurement wavelength was 227 nm except for CPO–Ca^{2+} complexes (303 nm).

containing CPO alone showed no significant absorption (remaining aqueous layer) when partitioned between octanol and water. This could be explained in the following terms: CPO is an ion-pair salt, which means that the drug can dissociate fairly easily in water leading to good solubility. However, when portioned between water and octanol it favors to maintain undissociated form in the lipophilic medium of octanol.

3.3. Determination of the solubility of CPO and its metal complexes in Tris–buffer (5 mM, pH 7.0)

The solubility of CPO was determined as described under the experimental section. The concentration of CPO in the supernatant (solubility) was determined using an equation obtained from the calibration curve measured at 322 nm at time of measurement. Accordingly, the average solubility of CPO in Tris–buffer was found to be 1 47mg/ml (R.S.D. = 10.79). For complexes, the solubility was determined by difference between the amount in precipitate and the total amount added as described in the experimental section. Table 3 summarizes the results obtained for the solubility of the different metal complexes. Table 3 shows that CPO metal complexes exhibit different aqueous solubilities from 0.09 mg/ml for iron complexes to 1.68 mg/ml for calcium and magnesium complexes. It is noteworthy that the solubility of the alkaline earth divalent metal complexes (calcium and magnesium) was identical and significantly higher than those for the transition metal complexes. Only alkaline earth metal complexes with CPO were more soluble (marginally) than CPO. Transition metal complexes of CPO were significantly less soluble than the CPO. However, it is noteworthy that the comparison here is being made with CPO rather than CPO-free acid. As pointed out earlier, CPO is an ion-pair salt for the acid CPO which makes it significantly more water-soluble. Therefore, the solubility of complexes, which is generally less than that of CPO, is expected to be better than that of CPO-free acid. Nevertheless, metal complexes to CPO could provide a means to manipulate the solubility of the drug.

3.4. Determination of the apparent partition coefficient of CPO and its metal complexes

Preliminary experiments have shown that direct measurement of CPO in the aqueous buffer was im-

Table 3
Average values ($n = 3$) and relative standard deviation for obtained solubility of CPO–metal complexes

Complex	Solubility (mg/ml)	*r* (standard deviation)
CPO–Mg^{2+}	1.68	3.62
CPO–Ca^{2+}	1.68	0.31
CPO–Cu^{2+}	0.16	1.49
CPO–Zn^{2+}	0.14	8.14
CPO–Mn^{2+}	0.12	1.67
CPO–Fe^{2+}	0.09	7.24

Table 4
Partition coefficient of CPO–metal complexes

Complex	Average partition coefficient	*r* (standard deviation)
CPO–Mg^{2+}	1.86	3.65
CPO–Ca^{2+}	1.89	3.81
CPO–Cu^{2+}	0.20	1.75
CPO–Zn^{2+}	0.72	1.50
CPO–Mn^{2+}	25.39	27.06
CPO–Fe^{2+}	4.10	13.58

practical, as only very little amount of CPO or its complexes remained in the aqueous layer when partitioned between two phases. Therefore, the drug was determined in the organic layer and the amount in the aqueous buffer was determined by difference between the total amount used of drug and that found in the organic layer. Accordingly, the estimated partition coefficient for CPO was 3.42 (R.S.D. = 8.97). As was the case with CPO, no detectable concentrations of the complexes were obtained in the aqueous buffer. Therefore, the amount of the complex in the organic layer was determined first, and then the amount remaining in the aqueous buffer was estimated by difference. Table 4 summarizes the results as average values of partition coefficients together with relative standard deviation (R.S.D.). The results show that the complexation process had effected the partitioning of the drug in the form of complex. For CPO, as such, the partition coefficient obtained was 3.42 whereas for the complexes, some had lower partition coefficient and others had higher values than that of the drug alone. For example the CPO–Mg^{2+} complex had a partition coefficient value lower than that of the drug alone (1.86); in other words, it became more hydrophilic than the drug itself. This is consistent with the previous result where CPO–Mg^{2+} complex had higher solubility in the aqueous buffer.

On the other hand, CPO–Mn^{2+} complex had a significant increase in the partition coefficient (25.39), meaning it became more lipophilic in nature than the drug alone, which also agrees with the results obtained in the solubility experiment. For the complexes of the three metals Cu^{2+}, Fe^{2+} and Zn^{2+}, the estimated apparent partition coefficients correlated well with the solubility (Fig. 6) where octanol–water apparent partition coefficient decreased linearly (correlation coefficient = 0.97) with obtained aqueous solubility. CPO–Mn^{2+} complex appeared to deviate slightly from this trend. The similarity in partition and aqueous

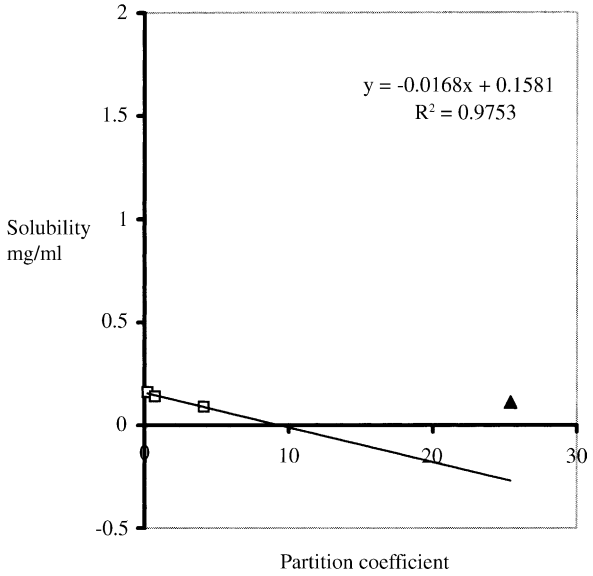

Fig. 6. Plot of solubility (mg/ml) against the apparent partition coefficient of complexes. (◯) Represents CPO–Mg^{2+} and CPO–Ca^{2+} complexes. (▲) Represents CPO–Mn^{2+} complex and (□) represents CPO–Cu^{2+}, CPO–Zn^{2+} and CPO–Fe^{2+} complexes. Note that CPO–Mg^{2+} and CPO–Ca^{2+} complexes have almost the same coordinates and their solubilities are well away from the range exhibited by other complexes.

solubility for CPO–Ca^{2+} and CPO–Mg^{2+} complexes was striking. Both complexes exhibited almost identical apparent partition coefficient and aqueous solubility; their apparent partition coefficient lied almost intermediate within the range of the tested complexes. However, both complexes (CPO–Mg^{2+} and CPO–Mn^{2+}) exhibited the highest water solubility of the examined complexes. Their aqueous solubilities were well away from that of other complexes (Fig. 6). This observation stresses the significant difference in the complexation behavior of these metals from other studied metals, and accords with the fact that both metals belonged to alkaline earth group of metals while other studied divalent metals were of transition metal type.

Overall, the complexation process was shown to affect the hydrophilic–lipophilic balance of CPO, which could be of use in the development of more effective formulations. However, if the metal complexes of CPO were to be used in pharmaceutical preparations instead of CPO, then the complexes must show comparable antifungal activity. A systematic study of the antifungal activity of the complexes against wide range of mi-

croorganisms is being carried out and is to be published separately.

4. Conclusion

CPO metal complexes (Mg^{2+}, Ca^{2+}, Cu^{2+}, Fe^{2+}, Zn^{2+} and Mn^{2+}) have been prepared and characterized using IR, UV, DSC, and melting point determination. CPO metal complexes were found to have a range of water solubility and lipophilicity ranging from well below that of CPO itself to marginally higher than that of CPO. These findings suggest that CPO–metal chelate formation might be used as a method to alter the physicochemical properties of the drug (polarity) to enable better formulation, and thus, better drug delivery. However, further microbiological studies are necessary to investigate the microbiological activity of the complexes.

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