Abstract:
In this work we present the synthesis and spectroscopic determination of CuII, coordinate compound with the antibiotic metronidazole. An accurate method was chemically designated for the determination of metronidazole in pharmaceutical preparations. The green complex that was formed between copper(II) and metronidazole was studied in methanolic media. Coordination to metal ions is through its imidazolic nitrogen, while the hydroxyl and nitro groups act as supramolecular synthons. Pleated sheet or layers are formed by \([\text{Cu(metronidazole)}_2\text{Cl(H}_2\text{O)}]\text{Cl}\). The new analytical method based on measuring absorbance in UV-visible spectrum at \(\lambda_{\text{max}}\) 400nm. Optimum pH and divalent copper ion concentration were estimated. Linearity(2×10^{-3} - 6×10^{-7}), detection limit 6×10^{-7} M. were determined. The complex was identified with UV-visible and FT-IR spectra. The molar ratio also investigated and found 1:2(Cu: Metr).

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Introduction:
Due to the selective toxicity to anaerobic bacteria and protozoarium, metronidazole (MTZ) has been found to be clinically useful in a variety of anaerobic and protozoarium infection, particularly *Trichomonas Vaginalis* and *Amoebic Dysentery* [1]. It can kill or inhibit the majority of anaerobic bacteria when the metronidazole concentration in serum is in the range from 2 to 8 μg/ml [2]. Therefore, the determination of trace levels of MTZ is very necessary in clinics.

Various methods, such as non-aqueous titration [3], spectrophotometry [4], high-performance liquid chromatography [5], polarography [6] and adsorptive stripping voltammetry [7], have been developed for this purpose.

Experimental:
Materials and Method:
The chemicals used in this work were obtained from B.D.H. and they were all pure grade reagents. FTIR spectra were recorded using shimadzu - 8000 spectrophotometer for the range 4000 – 200 cm⁻¹. Electronic spectra were recorded using shimadzu uv –visible spectrophotometer type 160A.

Standard Solutions:
Stock solution of metronidazole (1000ppm) was prepared in distilled water.

Stock solution of Copper (1000ppm) from CuCl₂·H₂O was prepared in distilled water.

Optimum conditions for the complex
1: Concentration of metal ion: Optimum concentration of the metal ion determined by the additions of 0.2- 0.4 mL of 1000ppm solution of metal ion to 4mL of 1000ppm metronidazole then extracting the complex after each addition and measuring the absorbance at λmax = 400nm (as shown in fig.1).

2: Effect of Temperature: Optimum temperature degree for the complex were determined by changing the temperature of solution
(30 C° to 80C°) and extracting the complex and measuring the absorbance at λmax =400nm and pH = 4 (as shown in fig.2).

3: Molar ratio of metal to metronidazole (M:L): (By using the Mole-Ratio method), the addition of 1mL (0.002M) standard metal solution to the same concentration of metronidazole solutions (1, 1.5, 2, 2.5, 3)mL then extracting the complex and measuring the absorbance at λmax =400nm, (as shown in fig.3).

Preparation of Standard Curve:
The complex was standardized by the reaction of (0.1-1mL) 1000ppm metronidazole standard solution with 1000ppm (0.5mL) Cuppric chloride standard solution and extracting the complex and measuring the absorbance at λmax =400nm (as shown in fig.4).

Extraction Procedure:
Sample Preparation
An amount of 10 pharmaceutical tablets of MTZ were ground into powder. The resulting powder was then extracted with 25 ml of buffer solution (pH 4.3). After being extracted, the extract filtered was into a calibrated flask and then diluted to 1000 ml for determination. The complex was synthesized by the reaction of metronidazole solution with copper ion solution, then extraction of complex by methanol and measure the absorbance at λmax, 400nm.

Results and Discussion
The Copper ion react hardly with the ligand in molar ratio 1:2. The molar ratio 1:2 produce the crystal of the complex [Cu(metronidazole)_2 Cl(H_2O)]Cl in methanolic medium. The crystal of the complex is soluble in pH 4 and denaturated at pH 6 over .

The chemical structure of the ligand (metronidazole) has more than one coordination center because there is imidazolic nitrogen, hydroxyl and nitro groups. When we compare the IR spectrum of ligand with that of complex we found:
1: The evidence for complexation is the band at 453cm⁻¹ for the connection of metal with oxygen, and there is another band at 427.5cm⁻¹ for the coordination of metal with nitrogen.
2: Changing of carbonyl band from 1721 cm\(^{-1}\) (in the ligand) to 1679.3 cm\(^{-1}\) (for the complex) at that may be refer to the stability of the carbonyl.

3: Appear of band at 3396.7 may be refer to coordination of H\(_2\)O with the metal

**Table 1: The IR spectrum (cm\(^{-1}\)) of the ligand and the complex.**

<table>
<thead>
<tr>
<th>Com.</th>
<th>C-H\text{arom}</th>
<th>C-H\text{alif}</th>
<th>C=C</th>
<th>C=N</th>
<th>C=O</th>
<th>Cu-O</th>
<th>Cu-N</th>
<th>NO\text{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ligand</td>
<td>3151.79</td>
<td>2981.3</td>
<td>1610.1</td>
<td>1556.61</td>
<td>1721</td>
<td>-</td>
<td>-</td>
<td>1406.15</td>
</tr>
<tr>
<td>Complex</td>
<td>3120.2</td>
<td>2870</td>
<td>1600</td>
<td>1550.9</td>
<td>1679.3</td>
<td>453</td>
<td>427.6</td>
<td>1400.2</td>
</tr>
</tbody>
</table>

Metronidazole react with Cu(II) in medium in molar ratio M:L\(_2\) at the pH = 4.3 to give green crystal of the complex [Cu(metronidazole)\(_2\)Cl(H\(_2\)O)] Cl. The complex decomposed at pH = 6.

**Table 2: The wave length and ABS of the ligand and the complex.**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Wave length(nm)</th>
<th>Abs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ligand</td>
<td>399</td>
<td>0.761</td>
</tr>
<tr>
<td>Mtr.</td>
<td>310</td>
<td>2.013</td>
</tr>
<tr>
<td></td>
<td>275</td>
<td>1.211</td>
</tr>
<tr>
<td>Complex</td>
<td>524</td>
<td>0.071</td>
</tr>
<tr>
<td>Cu(Met.)(_4)</td>
<td>401</td>
<td>0.620</td>
</tr>
<tr>
<td></td>
<td>360</td>
<td>2.011</td>
</tr>
<tr>
<td></td>
<td>255</td>
<td>1.55</td>
</tr>
</tbody>
</table>

**Optimum conditions for the complex**

1: **Concentration of metal ion:** Optimum concentration of the metal ion determined as it found form Figure1 (Concentration vs absorbance). The best concentration were given from the highest absorbance, and found to be 3.
2: **Temperature**: Optimum Temperature ($C^0$) of the complex formation determined as it found from Figure 2 (Temperature vs Absorbance). The best temperature ($t=30 \, C^0$) were given from the highest absorbance.
3: Molar ratio of metal to Metronidazole (M:L): The Mole-Ratio of metal ion to the metronidazole (in the complex) is found from Figure 3 (Volume vs Absorbance) at $\lambda_{\text{max}} = 400$ nm.

![Molar ratio of metal to metronidazole](image)

Figure 3: Molar ratio of metal to metronidazole at $(2 \times 10^{-3} \text{M})$, show that M:L equal to 1:2

**Standard Curve For our complex:** Fig.4 represent the concentration of metronidazole vs absorbance under Beer Law, Showing the linearity.

![Standard curve for our complex](image)
Determination Of Metronidazole In Pharmaceutical Preparations

Hamdan Abbood Al-Hamdany

Figure 4: Standard curve or determination of metronidazole in pharmaceutical preparations at $\lambda_{\text{max}} = 400$ nm.

Table 3: The $\lambda_{\text{max}}$, Linearity, D.L., S. And E. Of the complex.

<table>
<thead>
<tr>
<th>$\lambda_{\text{max}}$(nm)</th>
<th>Linearity M</th>
<th>Detection limit</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>1<em>10^{-3}-12</em>10^{-3}</td>
<td>1*10^{-3} M</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Table 4: The results of metronidazole determination in pharmaceuticals.

<table>
<thead>
<tr>
<th>Pharmaceutical</th>
<th>Stated</th>
<th>Found</th>
<th>Recovery %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met. indian</td>
<td>500mg</td>
<td>515mg</td>
<td>97%</td>
</tr>
</tbody>
</table>

Figure 6: The complex between Couper and Meronidazole
References