CHAPTER VI: ANTIBACTERIAL STUDIES OF COMPLEXES
In the ancient time, raw extracts of the plants were used for the amelioration of human suffering without knowing their chemical constituents and active principles. The importance of plant products and their utility encouraged human mind to find out the mysteries and marvels of biogenic processes. For attaining this aim drugs have been thoroughly investigated throughout the ages and it was noticed that several metal complexes with a drug possess more medicinal importance as compared to the corresponding drug.

The last few years have also seen the isolation of some wide spectrum drugs which have became very important due to their antimicrobial activity. Pathogens can be removed from the human body by complexation with life essential metals and the drug administered. With these ends, in view and to make an humble contribution to a distant goal, the author has studied the chemical nature and the antimicrobial activity of some important drug complexes with life essential metal ions against human pathogens.

Metal complexes are well known for their biological activity. The chemistry of life involves in an essential
way, some chemical elements including metals.\textsuperscript{3,4} The importance of sodium, potassium, calcium, iron, etc. has been well recognised. Examples in blood, haemoglobin an iron complex of protein is present.\textsuperscript{5} A number of metal ions are essential for life process, some are present in the structural units of our body while others are used in metabolic activities in the form of enzyme. Many enzymes contain metals and removal of metal can inactivate the enzyme. Trace amount of Ca, Zn, Co, Fe, etc. are necessary for life processes.\textsuperscript{6,7} Cobalt is present in vitamin B\textsubscript{12}, copper occurs in enzyme tyrosinase, zinc in carbonic anhydrase, magnesium in chlorophyll, iron in haemoglobin. The stagilization of insulin with zinc, the enzymatic bond formation and rupture processes of carbohydrates and nucleoproteins are also examples of systems in which metal chelate complexes are essential for biological activity.\textsuperscript{8-12} Metal chelates prevent virus multiplication.\textsuperscript{13} The chelates of heavy metals with resorcyclic acid have shown to exhibit antirheumatic action.\textsuperscript{14} Investigation on the chelation reaction of the anticancer compound, Riboflavin\textsuperscript{15}, Folic acid\textsuperscript{16}, Thioquinine\textsuperscript{17}, Adenine\textsuperscript{18}, and the carcinogenic compounds 1 amino-2 naphthol\textsuperscript{19} have been reported and chelating properties have been discussed in the light of their anticancer activities.

Schuberst\textsuperscript{20} has suggested that the pharmacological
activity of some drugs is associated with the chelated transport of plasma.

Albert and co-workers\textsuperscript{21-23} have shown that 8-hydroxyquinoline exerts antifungal and antibacterial action through metal chelate formation.

Many scientists\textsuperscript{24-26} have studied the structural relationship in which the molecular formulae of drugs are directly related to their biological activity. Various organic compounds having medicinal importance have also been used for the purpose of complexation with metals.

A survey of literature reveals that many analgesic antipyretic, antibiotic, etc. drugs have been used for this purpose.\textsuperscript{27-38} Some drugs have increased activity when administered as metal complexes\textsuperscript{39,40} and many drug complexes with their growth.\textsuperscript{41} Study of the coordination compounds of drugs led to the investigation directed towards establishing the site(s) of metal binding in the drug.\textsuperscript{42-47}

Shrivastava and co-workers have reported antibacterial activity of some Mg(II), Co(II), Ni(II) and Cu(II) complexes.\textsuperscript{48} Although, the role of metal binding in the mode of activity of tetracycline antibiotics is not settled at present, it is proposed that the amide carbaryl appears
to be essential for drug activity.\textsuperscript{49}

Sengupta and coworkers have investigated the nitrogen oxygen and sulphur containing heterocyclic rings and suggested that they may be potent antibacterial and antifungal agents.\textsuperscript{50} N, O and S containing heterocyclic compounds were tested in vitro for biological activity against \textit{Staphylococcus aureus}, \textit{Bacillus} and \textit{Salmonella} generic bacteria.\textsuperscript{51}

In this chapter the author has reported the results of antimicrobial activity of the complexes prepared with Fe(III) and Co(II).

Isolated complexes of drugs have been screened in vitro against the bacteria mentioned as under\textsuperscript{52-58}.

\textit{Escherichia coli}

It is gram negative motile bacillus producing acid and gas in lactose, is generally a harmless inhabitant of the bowel but it is a common cause of acute and chronic inflammation else where, especially when accompanied by other organisms. It may be responsible for acute inflammation in the appendix and gall bladder, in the pelvis of the kidney and in urinary bladder. The presence of \textit{E. coli} in
drinking water is strong evidence of pollution.

**Salmonella typhosa**

It is a gram negative natural pathogen of man, causing Typhoid. It contaminates the water, milk and food stuff to a large extent. It attacks on the chicks and some times leads to their death.

**Shigella flexneri**

It is gram negative bacteria and is the cause of bacillary dysentery. The organism gains entrance to the body by way of elimentary tract and produces toxin. Which is responsible for the direct injury to the intestinal walls. Dysentery is transmitted in the other man by water, milk, food and by direct contact.

**Bacillus pyocyaneus**

It is associated with disease condition both in man and animals. The organism is widely distributed in nature, being found in water, sewage. Some times on the normal skin and in infacted wounds. It may invade the nasal fossae, the middle ear, the meninges, the bronchi and other organs and set up seppuration. It is also a cause of intestinal disturbances, diarrhoea, abscess of liver,
pneumonia and desentery like diseases. In culture it forms a bluish green pigment.

**Evaluation of Antibacterial Activity**

Various methods\textsuperscript{59-67} are available for the evaluation of the antibacterial activity of different types of compounds. However in the present work, activities of the complex compounds were evaluated by the cup-plate Agar diffusion method.\textsuperscript{68} The main aim of these investigations was to study the changes in the activity with the variation in structure of drug molecules.

The cup-plate agar diffusion method consists of the following steps -

1. Preparation of the medium, its sterilization and tubing.
2. Treatment of the glass apparatus and its sterilization.
3. Pouring of the needed medium into sterilized petridishes and cutting of the cups.
4. Preparation of the required concentration of complexes and their pouring into the cups.
5. Incubation of particular temperature.

Out of the different steps in this method the most important is the selection of the suitable medium and its preparation, because it is the composition of the medium which exerts greatest influence upon the activity of a compound. The other factors which influence the tests are:

a. The kind and condition of the test organisms.
b. Concentration of the drug solution and site of action.
c. Environment factors which may augment or counteract the interaction of the drug and the parasite.
d. Temperature of the incubation because for each bacteria there is an optimal temperature and for most of the pathogenic bacteria this temperature is 37°C.
e. pH of the medium which is usually in the range of 7.2 to 7.6.
Experimental

Culture Medium

In the present work, with the above mentioned bacteria the nutrient agar medium is employed which has the following composition.\textsuperscript{71,72}

- Peptone \( \ldots 5 \text{ gm} \)
- Beef extract \( \ldots 3 \text{ gm} \)
- Agar-Agar \( \ldots 20 \text{ gm} \)
- Sodium chloride \( \ldots 5 \text{ gm} \)

For the preparation of the medium all the above ingredients except agar-agar were weighed are dissolved in water (500 mL) by gentle heat. After the ingredients were dissolved completely, more distilled water (500 mL) was added. Then the agar-agar was added to this solution and the mixture autoclaved for half an hour at 20 \( \frac{1}{2} \) lbs/sq.inch steam pressure. The hot medium was filtered. All glass apparatus was cleaned with chromic acid and then sterilized by keeping in an oven.

After autoclaving, it was cooled to 50°C and homogeneous suspension was prepared by transferring aseptically a few loopfuls of the spores of the corresponding microorganism from the fresh sub-culture into the nutrient agar
medium, followed by vigorous shaking. 20 mL of this medium was poured into each sterilized petridish and allowed to gel. After gelling the medium the disc (6 mm) was prepared with the help of a sterilized corkbouer in seeded agar plates. 73 0.1 mL of the test solution of different dilutions and control (metal) solution were dropped into the disc with help of sterilized pipette, petriplates were incubated at 37°C for 24 hours. The inhibition zone for each solution was observed in mm, which has been recorded in tables 6.1 to 6.12.

Results and Discussion

The zone of inhibition of the complexes against a number of gram positive and gram negative pathogens was recorded for 24 hours at 37°C. An important observation is the fact that all the mentioned drugs exhibit nearly similar activity as compared to control against all tested bacteria.

Sodium Valproate Complexes:

A study of the results Table 6.1 and 6.2 indicates that the complexes of Fe(III) and Co(II) with the titled drug exhibit very good to fairly good activity against many test organisms. The concentration of complexes
0.002M has been found to be quite active against *Bacillus pyocyaneus* (gram positive bacteria) *Salmonella typhosa*, *E. coli* and *Shigella flexneri* (gram negative bacteria). An outstanding achievement of the present study lies in the results obtained with Fe(III) and Co(II) sodium valproate complexes against all gram negative and gram positive organisms under study. All organism shows negative percentage change over control.

**Piroxicam complexes:**

It is clear from the data (Table 6.3 and 6.4) that the complexes of Fe(III) and Co(II) with this drug exhibit good activity against all test organisms and shows negative percentage change over control. The activity however, decreases on serial dilutions.

**Flurozepam Hydrogen Chloride Complexes:**

Both complexes shows a negative percentage change over control it is nearly -50%. Both complexes shows good activity against all gram positive and gram negative organisms under study. It is clear from the data (Table 6.5 and 6.6).
Diclofenac Sodium:

From the study of the data (Table 6.7 and 6.8) it is observed that the complexes of Fe(III) and Co(II) with this drug shows good activity against all organisms under study. The percentage over control is negative and it is near about - 56%.

Cefadroxil Complexes:

Fe(III) and Co(II) complexes with this drug exhibits good activity against all gram positive and gram negative organisms. The percentage over control is negative and is near about - 60%. The activity however, decreases on serial dilutions (Table 6.9 and 6.10).

Norfloxacin Complexes:

These complexes also shows same results with others. It is clear from the data (Table 6.11 and 6.12). Both complexes exhibits good activity against all four organisms under study. The percentage over control is negative and is near about - 50%. The activity however, decreases on serial dilutions.
Conclusion

With the above findings it could be concluded that Fe(III) and Co(II) complexes with the drugs under study, were found to be bacterial toxic, although in varied degrees. One more important fact which is evident from the data that the microbial activity is a function of the concentration of complexes. The antibacterial activity of the complex increases with the increase in its concentration. These findings are very well supported by those reported in the literature.74-76.

Some complexes have strong antibacterial efficacy against various susceptible test bacteria, which are mostly human pathogens and may be exploited as bacteriocides for controlling infections caused by the test microorganisms.
Table 6.1. Antibacterial Activity of Fe(III) Sodium Valproate Complex.

Inhibition zones (mm) includes the diameter of well 6 mm.

Bacteria was incubated at 37°C for 24 hours after seeding in nutrient agar medium.

<table>
<thead>
<tr>
<th>Concentration of complex in moles</th>
<th>Organisms</th>
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<td>Shigella flexneri</td>
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* Concentration of control metal Fe(III) in moles.

** Percentage change over control.
Table 6.2. Antibacterial Activity of Co(II) Sodium Valproate Complex.

Inhibition zones (mm) includes the diameter of well 6 mm
Bacteria was incubated at 37°C for 24 hours after seeding in nutrient agar medium.

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<th>Concentration of complex in moles</th>
<th>Escheriachia coli</th>
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* Concentration of control metal Co(II) in moles.
** Percentage change over control.
Table 6.3. Antibacterial Activity of Fe(III) Piroxican Complex.

Inhibition zones (mm) includes the diameter of well 6 mm

Bacteria was incubated at 37°C for 24 hours after seeding in nutrient agar medium.

<table>
<thead>
<tr>
<th>Concentration of complex in moles</th>
<th>Escherichia coli</th>
<th>Salmonella typhosa</th>
<th>Shigella flexneri</th>
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<td>% change **</td>
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* Concentration of control metal Fe(III) in moles

** Percentage change over control.
Table 6.4. Antibacterial Activity of Co(II) Piroxicam Complex.

Inhibition zones (mm) includes the diameter of well 6 mm

Bacteria was incubated at 37°C for 24 hours after seeding in nutrient agar medium.

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<th>Concentration of complex in moles</th>
<th>Escherichia coli</th>
<th>Salmonella typhosa</th>
<th>Shigella flexneri</th>
<th>Bacillus pyocyaneus</th>
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<td>% change**</td>
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<td>-50</td>
<td>-42</td>
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* Concentration of control metal Co(II) in moles.

** Percentage change over control.
Table 6.5. Antibacterial Activity of Fe(III) Flurazepam Hydrogen Chloride Complex.

Inhibition zones (mm) includes the diameter of well 6 mm.

Bacteria was incubated at 37°C for 24 hours after seeding in nutrient agar medium.

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<tr>
<th>Concentration of complex in moles</th>
<th>Escherichia coli</th>
<th>Salmonella typhosa</th>
<th>Shigella flexneri</th>
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<td>-36</td>
<td>-38</td>
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* Concentration of control metal Fe(III) in moles.
** Percentage change over control.
Table 6.6. Antibacterial Activity of Co(II) Flurazepan Hydrogen Chloride Complex

Inhibition zones (mm) includes the diameter of well 6 mm.
Bacteria was incubated at 37°C for 24 hours after seeding in nutrient agar medium.

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<th>Inhibition zone in mm</th>
<th>Escherichia coli</th>
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<th>Shigella flexneri</th>
<th>Bacillus pyocyaneus</th>
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* Concentration of control metal Co(II) in moles.
** Percentage change over control.
Table 6.7. Antibacterial Activity of Fe(III) Diclofenac Sodium Complex.

Inhibition zones (mm) includes the diameter of well 6 mm.

Bacteria was incubated at 37°C for 24 hours after seeding in nutrient agar medium.

<table>
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<tr>
<th>Concentration of complex in moles</th>
<th>Escherichia coli</th>
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<th>Shigella flexneri</th>
<th>Bacillus pyocyaneus</th>
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* Concentration of control metal Fe(III) in moles
**: Percentage change over control.
Table 6.8. Antibacterial Activity of Co(II) Diclofenac Sodium Complex.

Inhibition zones (mm) includes the diameter of well 6 mm.

Bacteria was incubated at 37°C for 24 hours after seeding in nutrient agar medium.

<table>
<thead>
<tr>
<th>Concentration of complex in moles</th>
<th>Escherichia coli</th>
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<td>% change**</td>
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* Concentration of control metal Co(II) in moles.
** Percentage change over control.
Table 6.9. Antibacterial Activity of Fe(III) Cefadroxil Samples.

Inhibition zones (mm) includes the diameter of well 6 mm

Bacteria was incubated at 37°C for 24 hours after seeding in nutrient agar medium.

<table>
<thead>
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<th>Concentration of complex in moles</th>
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<tbody>
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<td>Escherichia coli</td>
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<td>% Change**</td>
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</tbody>
</table>

* Concentration of control metal Co(II) in moles.

** Percentage change over control.
Table 6.10. Antibacterial Activity of Co(II) Cefadroxil Complex.

Inhibition zones (mm) includes the diameter of well 6 mm.

Bacteria was incubated at 37°C for 24 hours after seeding in nutrient agar medium.

<table>
<thead>
<tr>
<th>Concentration of complex in moles</th>
<th>Escherichia coli</th>
<th>Salmonella typhosa</th>
<th>Shigella flexneri</th>
<th>Bacillus pyocyaneus</th>
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</thead>
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<td>% change**</td>
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* Concentration of control metal Co(II) in moles.

** Percentage change over control.
Table 6.11. Antibacterial Activity of Fe(III) Norfloxacain Complex.

Inhibition zones (mm) includes the diameter of well 6 mm.

Bacteria was incubated at 37°C for 24 hours after seeding in nutrient agar medium.

<table>
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* Concentration of control metal Fe(III) in moles.
** Percentage change over control.

Inhibition zones (mm) includes the diameter of well 6 mm.

Bacteria was incubated at 37°C for 24 hours after seeding in nutrient agar medium.

<table>
<thead>
<tr>
<th>Concentration of complex in moles</th>
<th>Escherichia coli</th>
<th>Salmonella typhosa</th>
<th>Shigella flexneri</th>
<th>Bacillus pyocyaneus</th>
</tr>
</thead>
<tbody>
<tr>
<td>.002</td>
<td>22</td>
<td>22</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>.0015</td>
<td>20</td>
<td>21</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>.001</td>
<td>17</td>
<td>15</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>% change**</td>
<td>-54</td>
<td>-57</td>
<td>-49</td>
<td>-40</td>
</tr>
</tbody>
</table>

* Concentration of control metal Co(II) in moles.
** Percentage change over control.
REFERENCES


60. Marrow G. and Berry G.P., J. Bact., 1938, 38, 290.


SUMMARY