“SPECTRAL STUDIES ON METAL CHELATES WITH SOME PHARMACOLOGICALLY SIGNIFICANT COMPOUNDS”

SCOPE OF THE PRESENT WORK

Reports on metal complexes of many drugs of choice in the treatment of various diseases like rheumatoid arthritis, bronchial asthma, anemia, Wilson’s disease, cancer, etc., are appearing regularly in the chemical literature. In several instances it was shown that the metal complexes are more effective and less toxic than the parent drugs. So it was considered interesting and useful to study the metal complexes of drugs using various physico–chemical methods.

It is proposed to study the metal binding characteristics of some selected pharmaceuticals mentioned below.

Thiacetazone (p–acetamidobenzaldehyde thiosemicarbazone), an anti–tuber–culosis drug is containing acetamido carbonyl oxygen, hydrazine nitrogen, carbothioamide nitrogen and –sulphur as possible key atoms to bind the metal ions.

Sulfanilamide drugs such as sulfamethoxazole and sulfisoxazole are used as urinary antiseptics. In these heterocyclic derivatives of sulfanilamide, isoxazole ring nitrogen is also there in addition to aniline nitrogen, sulfonamide nitrogen and sulfonyl oxygen, capable of binding metal ions of interest. Nitrofurantoin, a 5–nitrofurfural derivative of imidazolidine–2,4–dione, is another urinary antiseptic found interesting to study its metal coordination behaviour under controlled experimental conditions.

N–Bis(2–hydroxyethyl)glycine, commonly known as bicine, is potential chelating compound containing hydroxyl oxygen, carboxyl oxygen and tertiary nitrogen as key atoms.
Dapsone (4,4′-diaminodiphenylsulfone) is a popular anti-leprosy drug containing two aniline NH₂ groups for metal binding.

In addition to biologically important metals like magnesium, iron, cobalt, copper, zinc, etc., other metals such as manganese, nickel, cadmium, mercury and lead are also included in the preparation of complexes of the pharmaceuticals mentioned above. This enables us to characterize the metal complexes prepared effectively, using various techniques such as UV–Visible, infrared and proton magnetic resonance spectral analyses, magnetic susceptibility measurement and thermal decomposition study.

The significance of copper complexes of biologically active or inactive organic compounds in medical pharmacology prompted us to prepare some mixed ligand copper(II) complexes of salicylamide, acetylsalicyclic acid, isonicotinic acidhydrazide, pyridoxine, pyrazinamide and theophylline.

The main objective of the present study is to understand the conditions under which the selected pharmaceuticals form metal complexes and to throw light on the metal binding nature of these biologically important compounds. Detailed study of any single complex using methods such as ESR, X–ray and polarized spectra is beyond the scope of this work and no attempt would be made to analyse completely the electronic and infrared spectra of any complex.

The integrity, maintenance and functioning of the mammalian body depend on the presence of sodium, potassium, magnesium, calcium and traces of other metals including iron, cobalt, copper, zinc, manganese and molybdenum. Because of their interactions with binding groups on proteins, heavy metal ions like that of mercury, lead, silver, and arsenic are potent enzyme inhibitors exerting toxic effects on living systems. The applications of chelating agents in the medical sciences have expanded considerably from their early use in the decorporation of toxic elements.
This expansion in use has occurred with improvements in knowledge of inorganic biochemistry.

Many pharmaceutical compounds currently in use have chelating ability and metal complexes of such compounds have been the subject of research interest for bio–inorganic chemists. In the present study, metal complexes of certain drugs are prepared and the results of various physico–chemical methods of analysis are discussed. The metal binding characteristics of the drugs used in this study are highlighted with the available evidences from those characterization techniques adapted.

The whole work has been divided into six chapters. In the first chapter, Introduction the significance of chelating agents in medicine is highlighted with a brief account of coordination behaviour of various drugs currently in use to treat many diseases.

**Chapter–II: Materials and Research Methodology:**

The description of research methodology adapted and a brief mention about the nature and source of the various starting materials employed constitute the second chapter. It includes the general experimental procedures for the preparation of metal complexes of selected drugs.

A detailed discussion on magnetic, spectral and thermal properties of metal complexes of thiacetazone, an antituberculosis drug, is given in this chapter.

**Chapter–III: Metal Complexes of 2–\[\{(4–Acetyl amino) phenyl\} methylene\] Hydrazine Carbothioamide (Thiacetazone)**

The metals studied include cobalt, nickel, zinc, cadmium and mercury. Thiacetazone is shown to bind the metal ions through thione/thiol sulfur and hydrazine nitrogen atoms. The proton magnetic resonance spectral study on diamagnetic complexes revealed that the ligand is not deprotonated on complex
formation. The metal complexes isolated from acetone solution are shown to have octahedral stereochemistry with composition of the type $\text{ML}_n\text{X}_2$, where $\text{M}$ is the divalent metal ion, $\text{L}$ is 1 or 2 molecules of the neutral ligand and $\text{X}$ is the anion like $\text{Cl}^-$, $\text{Br}^-$, $\text{NO}_3^-$, CNS$^-$, etc. Some of these complexes like cadmium(II) and mercury(II) chloride complexes are found to be insoluble in many solvents indicating polymeric nature of these compounds.

**Chapter IV: Metal Complexes of Urinary Antiseptics:**

In this chapter the structural features of metal complexes of some urinary antiseptics prepared are discussed. Of the three pharmaceuticals, sulfamethoxazole and sulfisoxazole are sulfonamide derivatives containing isoxazole moiety.

**4.1 Metal Complexes of 4−Amino−N−(5−Methyl−3−Isoxazolyl) Benzene Sulfonamide (Sulfamethoxazole)**

Sulfamethoxazole is shown to form metal complexes of the type $\text{ML}_n\cdot\text{xH}_2\text{O}$ in which the ligand remains deprotonated. Various spectral data including infrared, UV−Visible and proton magnetic resonance and magnetic moment values are given with detailed discussion. The participation of isoxazole ring nitrogen in binding the metal ion is explained with evidence in the case of copper(II) complex. In the case of other metal complexes, the sulfonyl oxygen is shown to involve in binding the metal ion either weakly or strongly. Sulfamethoxazole is found to behave essentially as a bidentate ligand, though polymerization of the complex with additional metal−ligand bonds seems to be feasible.

**4.2 Metal Complexes of 4−Amino−N−(3,4−Dimethyl−5−Isoxazolyl) Benzenesulfonamide (Sulfisoxazole)**

In the case of metal complexes of sulfisoxazole, the isoxazole moiety remains free of metal coordination. Sulfisoxazole is shown to act either as
monodentate or bidentate ligand with the deprotonation of sulfonamide NH group. The participation of aniline NH$_2$ group in metal binding is not evident from the infrared spectral study on the metal complexes prepared.

4.3 **Metal Complexes of 1−[{(5−Nitro−2−Furanyl) Methylene} Amino]−2,4−imidazolidine dione (Nitrofurantoin)**

Nitrofurantoin is another urinary antiseptic drug shown to bind metal ions under alkaline reaction condition. It is found to form neutral complexes with divalent metal ions. Under the experimental conditions, the dione form of nitrofurantoin changes into enol form and reacts with the metal ions to form complexes of the type [ML$_2$(H$_2$O)$_4$]$_n$H$_2$O. Infrared spectral study showed that the ligand binds the metal ion only through alcoholic oxygen atom attached to the imidazole ring of the enol form. Thermal decomposition study on the metal complexes of nitrofurantoin revealed that there are two types of water molecules (water of hydration and coordinated water molecules) in the complexes.

**Chapter V: Metal Complexes of N−Bis (2−Hydroxy ethyl) Glycine (Bicine):**

Bicine, a derivative of glycine with two hydroxyethyl groups on the nitrogen atom can be a potential chelator. Complexes with magnesium, manganese, cobalt, copper, zinc and cadmium are isolated. The structural investigation on these metal complexes indicates the involvement of one or both alcoholic oxygen atoms in metal binding besides carboxylic oxygen and tertiary nitrogen atoms. The presence of free carbonyl group is also evident in the case of cobalt(II) and copper(II) complexes of bicine. The magnetic moments calculated for some of the metal complexes indicate the presence of electron spin interaction between two closer metal ions in the complex. These details are given in the chapter.
Chapter−VI:  Mixed Ligand Copper(II) Complexes of Some Drugs and Metal Complexes of 4,4′−Diamino Diphenyl Sulfone (Dapsone):

Mixed ligand copper(II) complexes of some drugs and adducts of dapsone, an anti−leprosy drug, with chlorides of nickel(II), copper(II) and zinc(II).

A binuclear copper(II) complex of isoniazid (an antituberculosis drug) and pyridoxine (Vitamin B₆) is isolated. The green coloured complex is shown to contain one acetate anion besides two water molecules. A mixed ligand copper(II) complex of isoniazid and pyrazinamide (both are anti−tuberculosis drugs) is shown to be polymeric with possible involvement of ring nitrogen atoms of both ligands in metal coordination. Acetylsalicylic acid (aspirin) and theophylline sodium are shown to react with copper(II) ions forming possibly a polymeric complex containing one water molecule. Salicylamide, an analgesic, is shown to exhibit linkage isomerism in the binuclear copper(II) complexes containing hydroxyl bridges. The role of amide nitrogen and carbonyl oxygen in metal binding signifies the linkage isomerism in these complexes.

The analytical and physico−chemical data for metal−dapsone compounds show that the composition is of 1:2 stoichiometry. These compounds are found to be essentially adducts of metal chlorides with weak interactions between dapsone and the metal ions like copper(II), zinc(II) and nickel(II).