Abstract of the thesis entitled

"STUDIES IN METAL COMPLEXES OF PHARMACEUTICALLY IMPORTANT DRUGS"

Submitted

To

Dr. Babasaheb Ambedkar Marathwada University,
Aurangabad

For

The Degree of

DOCTOR OF PHILOSOPHY

in

CHEMISTRY

By

MR. SURESH TUKARAM GAIKWAD

Under the guidance of

Dr. B.R. Arbad,
Professor
Department of Chemistry,
Dr. Babasaheb Ambedkar Marathwada University,
Aurangabad.
Abstract of the thesis entitled
"Studies in Metal Complexes of Pharmaceutically Important Drugs"

INTRODUCTION

Drugs are naturally occurring or synthetic which contain oxygen or sulphur or nitrogen atoms in their functional groups. They form complexes with metal ions either initially or after metabolic changes in the body to form stable five or six membered rings. The medicinal properties of many chelating agent is related to their ability to form stable metal chelate ring. The metal complexes of drugs are found to be more potent than parent drugs. In view of the above considerations the metal chelating tendencies of various antibacterial, anticancer and antiviral drugs have been studied.

IMPORTANCE OF TERNARY COMPLEXES

The complex of different donor atoms when belong to separate molecules is called ternary complex. These complexes play a vital role in medicinal fields, toxicology, analytical chemistry and environmental science.

The drug used in the treatment of cancer is cis-platin i.e. cis-dichloro diamine Platinum(II). The anticancer activity of this complex arises due to the formation of another ternary complex in which two chloride ions are replaced by the N-7 guanines located adjacently on the DNA of the cancer
cell. In order to minimize side effects and to increase the anticancer effect, large number of novel ternary complexes have been synthesized and studied for anticancer activity.

The drug molecules proposed to be used are: (1) (S)-l-{N-[-(Ethoxy carbonyl)-3-phenyl propyl]-l-alanyl}-L-proline-maleate (Enalpril maleate) is an antihypertensive drug; (2) 2-diethyl-amino-2',6'-aceto-xylidide (lignocaine hydrochloride) which is a local anaesthetic; (3) a-[l-(Methylamino) - ethyl] - benzene - methanol - hydrochloride (Ephedrine hydrochloride), and (4) 3,7-Dihydro-l,3-dimethyl-lH-purine-2,6-dione (Theophylline) act as bronchodialators. Hence considering the significance of mixed ligand complexes in medical field it was considered to investigate the stability of binary and ternary metal complexes of the proposed drugs.

AIM OF THE PROPOSED WORK

The aim of the proposed work is to study in a quantitative manner the stability of biologically relevant binary and ternary complexes of the type ML, ML\textsubscript{2}, MR, MR\textsubscript{2}, MLR in aqueous media at 27°C and at ionic strength 0.1 M (NaClO\textsubscript{4}).

The work to be presented in the thesis is divided into three sections: First part deals with the study of binary and ternary complexes of drugs and amino acids with metal ions. Second part deals with the study of binary and ternary complexes drugs and peptides with metal ions. The third part deals
with the study of binary and ternary complexes of peptides and amino acids with metal ions.

Metal ions such as Co(II), Ni(II), Cu(II) and Zn(II) are chosen on the basis of their physiological and pharmacological importance.

Literature survey reveals that the formation, stability and structures of the binary and ternary complexes of the above ligands have not been comprehensively studied.

Part I : Primary ligands (L) drugs:
1) Enalpril Maleate
2) Lignocaine hydrochloride
3) Ephedrine hydrochloride
4) Theophylline

Secondary ligands (R) are amino acids:
1) DL-Alanine
2) Glycine
3) L-Isoleucine
4) L-Phenyl alanine
5) DL-Serine
6) DL-Valine
7) L-Tryptophan
8) L-Glutamic acid

Part II: Primary ligands (L) are drugs:
1) Enalpril Maleate
2) Lignocaine hydrochloride
3) Ephedrine hydrochloride
4) Theophylline

Secondary ligands (R) are peptides:
1) Glycil-glycine
2) Alanine-glycine
3) Glycil-glycil-glycine
4) Glycil-leuine
IMPORTANCE OF DRUGS

The majority of diseases are caused by microorganisms which enter into the body where they multiply very fast, overcome the body defenses and causes diseases. A substance which cures an ailment of symptoms is called drug. The action of drug is to remove toxic metal ions from bodies (metal poisoning) from the coordination behaviour. There are several types of drugs such as analgesics, tranquilizers, antiseptics, antibiotic, anaesthetic, antidepressant, sulpha drug and antipyretic. A majority of the naturally occurring or synthesis drugs contain functional groups with co-coordinating behaviour towards metal ions. Therefore in present work we have studied the complex behaviour of Enalpril maleate, Lignocaine HC1, Ephedrine HC1 and Theophylline with transition metal ions.

IMPORTANCE OF AMINO ACIDS AND PEPTIDES

Proteins are important and essential constituents of all living cells and constitute almost 50 percent of their dry weight. Proteins are polyamides formed from amino acids and peptides which constitute important constituent of food. There are different kinds of proteins and each one is specialized for specific biological function. Proteins are macromolecules, polymers of amino acids. Amino acids must be supplied in the diet, its deficiency leads to loss of weight and causes edema. Peptides and amino acids contain at least one amino (-NH$_2$) group and carboxylic (-COOH) group. It has good coordination sites for the metal complexation.
Therefore, present work incorporates the study of the complex behaviour of amino acids i.e. alanine, glycine, isoleucine, phenyl alanine, serine, valine, tryptophan, glutamic acid and peptides viz., glycil-glycine, alanine-glycine, glycil-glycil-glycine and glycil-lecuine.

**IMPORTANCE OF METALS**

Transition metal ions play an important role in biological system and are integral part of enzymes to trigger a reaction, control reaction mechanism, stabilize protein structure, maintain structure of cell walls etc. According to latest information regulation of metabolism and growth of cells depend on the mobilization of transition metal ions. Therefore in present work we have studied the complex behaviour of cobalt, nickel, copper and zinc.

**EXPERIMENTAL DETAILS AND CALCULATIONS OF RESULTS**

**pH METRY**

The pH metric titrations were carried out in a double walled titration cell provided with a combination of glass and calomel electrode. The temperature was maintained at 27°C by circulating water from the thermostat through the double walled jacketed cell. The ionic strength of the solution was maintained constant at \( \mu_\text{s} = 0.1 \) M by taking \( \text{NaClO}_4 \) as supporting electrolyte. An Elico pH meter model LI-120 of 0.01 accuracy
(0-14 pH) in conjunction with combined glass and calomel electrode was used for the measurement of pH values. The observed pH readings are compared with the actual hydrogen ion concentration calculated from the data tabulated by Harned and Owen. The pH regions below 3.5 and above 10.5 were calibrated by measuring in HCl and NaOH respectively.

The acid dissociation constants and the stability constants for the binary and mixed ligand complexes were determined by pH metric titration of the ligand in the absence and presence of the metal ion respectively with standard sodium carbonate free sodium hydroxide. The pH metric readings were noted after addition of small increments of standard sodium hydroxide to the cell. From the reading a graph of pH vs volume of base added were drawn. The titration curves give an indication of the composition of the metal complex formed. The stability constants were calculated by processing the pH metric data with the computer program "SCOGS".

In the determination of dissociation constant of the ligands, solution were prepared in aqueous medium. The concentration of the ligand taken was 0.01 M. In the determination of stability constant of binary complexes 1:5 molar ratio of metal to ligands were taken. The concentration of the metal ion solutions used was 0.01 M. The stability constants of the ternary complexes were determined using 1:1:1 molar ratio of the metal, primary ligand and secondary ligand.
CALCULATIONS

Protonation constant of free ligands, stability constant of binary complexes and ternary metal complexes were calculated using the computer program, SCOGS from pH-metric data. In addition to this, concentration of various species present as a function of pH were also computed from the known constant and are presented in the form of pH species profiles using the computer program SCOGS. The species distribution curves are useful in visualizing the nature and concentration of various species present in solution under a given set of experimental conditions.

RESULTS

1) ACID DISSOCIATION CONSTANTS

The acid dissociation constant of ligand Enalpril maleate, Lignocaine HC1, Ephedrine HC1 and Theophylline were investigated pH metrically at 27°C and n = 0.1 M NaClO$_4$. The pH metric data was analyzed by the computer program to evaluate the dissociation constant of drugs. Similarly the acid dissociation constant of various amino acids and peptides mentioned above were also re-determined under identical experimental conditions. Effect of substituents on the pK values is explained and calculated pK values are companed with literature values wherever possible.
2. **BINARY COMPLEXES OF METAL IONS**

   The stability constants of binary complexes of Co(II), Ni(II), Cu(II) and Zn(II) with Enalpril maleate, Lignocaine HC1, Ephedrine HC1 and Theophylline were investigated pH metrically at 27°C and $\mu = 0.1$ M NaClC$_4$. The stability constants were evaluated using the computer program. At the same time the binary stability constants of Co(II), Ni(II), Cu(II) and Zn(II) complexes with various amino acids and peptides were re-determined under identical experimental condition to permit accurate comparison.

3. **TERNARY COMPLEXES OF METAL IONS**

   Mixed ligand M(II) i.e. Co(II), Ni(II), Cu(II) and Zn(II) complexes containing drugs, amino acids and peptides were studied. Mixed ligand M(II) systems containing 1:1:1 molar ratio of drugs, amino acids and metals were taken and investigated pH metrically at 27°C and $\mu, = 0.1$ M NaClO$_4$ to determine the stability constants of MLR complexes. The influence of the ligand L and R on the stability of mixed ligand complexes were quantitatively assessed by the data processed with the computer program "SCOGS". The stability constant of the corresponding MLR were quantitatively compared in terms of the parameter $\Delta\log K$. 

8
PRESENT WORK

The present work entitled: Studies in metal complexes of pharmaceutically important drugs” is divided into four chapters.

Chapter I – It deals with the brief introduction, basic principles involved in coordination chemistry, literature survey pertaining to the proposed work, biological importance of amino acids, drugs and the metal ions used in the present work. The chapter concludes with the aims and objectives of the work and references.

Chapter II – It incorporates the studies of binary complexes of metal ions with drugs, amino acids and peptides. It is outlined in three parts: Part one deals with the brief interaction of formation of complexes in solution, characteristics of complexes, their stoichiometry and stability. Part two gives the mathematical and experimental details involved in pH metric titration technique. Part three describes the details of the results and discussion of binary complexes of drugs, peptides and amino acids with metal ions.

Chapter III – It incorporates the studies of ternary complexes of metal ions with drugs, peptides and amino acids. It is outlined in three parts.
Section-I starts with the introduction of ternary complexes, literature survey, factors governing the formation and stability of ternary complexes and the scope of such studies.

Section-II describes the mathematical conditions for the formation of ternary complexes, methods used in the study of these complexes, experimental methodology and the explanation regarding the use of computational facilities for the calculation of stability constants.

Section-III present the results and discussion of ternary complexes of Cobalt, Nickel, Copper and Zinc with drugs, peptides and amino acids in an aqueous medium. The chapter ends with the conclusion drawn from the present study and suggestions.
ORIGINAL WORK

The drugs used in this study have been used for the first time as chelating agents in aqueous medium with some transition metal ions like Co(II), Ni(II), Cu(II) and Zn(II).

These drugs are also used for the first time to study the formation of ternary complexes with amino acids and peptides as secondary ligands in aqueous medium.

The protonation constant of free ligands and stability constants of binary and mixed ligand complexes was determined. The stability constants were calculated by processing the pH meter data using computer program SCOOGS for studying concentration of various species present in solution.

Dr. B.R. Arbad
Research Guide

Mr. S.T. Gaikwad
Research Student