CHAPTER VI

SUMMARY AND CONCLUSION
In recent years it has increasingly apparent that proper balance of the biologically available metals like Cr, Mn, Fe, Co, Ni, Cu, Zn, Mo and Cd etc. is necessary for the efficient metabolism and growth of animal and plants. A slight change in the concentration of these metal ions brings about enormous changes causing various diseases. The metal also helps in the storage and transport of the drug in the body system through enzymes or amino acids. Sometimes the traces of transition metal ions present in the body may change the behaviour of enzyme system by replacing the essential metals. Due to replacement of essential metal the structure and function of the nucleic acid may also be effected. The drug changes its activity by combining with the metal ions. In this way, it is most expected that the traces of metals present in the body can help to transport the drug to the site of its physiological action.

Studies on metal complexes with other therapeutic agents suggested that drugs act as a chelate ligand and during the action of drug complex formation takes place and this favours the attachment of chelate with tissue and a metal atom acts as a bridge between drug and nucleic acid of the tissue. It has been reported that complexes of metallic salts are more potent and less toxic as compared to the parent drug. Some drugs have increased activity when administered as metal complexes. Various physico-chemical parameters of a drug and even above that structural variations may increase the therapeutic value of the compound by widening the gap between the therapeutic action and its side effects. In addition, certain structural modifications may enhance or uncover many dormant physiological and biochemical efficiencies of the drug.

Diclofenac sodium, mefenamic acid, flufenamic acid and piroxicam are non-steroidal antiinflammatory drugs and well known for their medicinal values. Detailed study on the survey of literature reveals that they have not
received a thorough, adequate and conclusive investigation in so far as their chemistry of coordination is concerned.

The present work deals with the investigations on the ligation aspects and change in biological activities of the taken drugs with the variation in the structure due to complexation with some transition metal ions like Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II) and Zn(II).

The thesis has been divided into six chapters.

CHAPTER -I

Chapter-I contains (i) General introduction of coordination compounds in many type of chemical and biological processes, (ii) Description of main coordination characteristics of metal drug complexes, (iii) Survey of literature on recent development in the coordination chemistry of their metallic complexes and (iv) Importance of the present studies.

The main coordination characteristics of some essential transition metal ions are their small cation size, large nuclear charge, lower coordination number predominantly covalent nature of metal-ligand bond and dominant role of entropy factor in stabilising their complexes and their 'hard acid' type behaviour in accordance with which they show preference for more electronegative donor atoms in coordination.

During the last two decades a number of metal-antiinflammatory drug complexes have been synthesised and characterized using mainly O-O- or O-N- donors but pure N-donors have also been successfully employed.

The metal ions studied in the present work include Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II) and Zn(II) i.e., mainly from 3-d transition elements. The drugs were from non-steroidal antiinflammatory group include: Diclofenac sodium, mefenamic acid, flufenamic acid and piroxicam.
CHAPTER – II

This chapter has been devoted traditionally to a brief description of physico-chemical methods employed in the present work i.e., molar conductance, magnetic moment measurements, electronic and infrared spectroscopy. Elemental analysis of the complexes has also been carried out.

CHAPTER – III

This chapter describes the various physico-chemical technique used in the present investigation. Isolation of the complexes and the experimental data has been incorported in this chapter. Water and organic solvents were used for the preparation of the complexes. Isolated complexes were purified and recrystallised employing standard methods. All the complexes were highly stable, insoluble in water and most of the common organic solvent.

CHAPTER – IV

This chapter comprises results and discussion. First part of this chapter describes in general, the stereochemistry of the complexes while the second part gives an account of the structural conclusions of individual drug complexes drawn on the basis of various physico-chemical data.

Diclofenac sodium complexes were isolated at pH 5-8. On the basis of various physico-chemical investigations it has been found that the drug diclofenac sodium behaves as a monoproptic bidentate ligand coordinating through nitrogen of >NH group and oxygen on COO− group. The Cr(III), Fe(III), and Zn(II) complexes were octahedral with 1 : 2 metal to drug ratio but Mn(II) complex has 1 : 1 ratio. Two/three coordination position are occupied by water molecules but in case of Fe(III) complex one coordination position is occupied by water molecule and another by hydroxy group. Presence of coordinated water molecules, OH− and CH3COO− groups has been
confirmed by IR data and elemental analysis. The presence of chloride ion in Cr(III) complex has been confirmed by elemental analysis.

Mefenamic acid complexes were isolated at pH 5-8. On the basis of various physico-chemical investigations it has been found that the drug mefenamic acid behaves as a monoproton bidentate ligand coordinating through nitrogen of >NH group and oxygen of COO⁻ group. The complexes were octahedral having metal to ligand stoichiometric ratio 1 : 2 for Cr(III), Fe(III), Ni(II), Co(II) and Zn(II) and 1 : 1 for Mn(II) and Cu(II). Two/three coordination positions are occupied by water molecules but in case of Fe(III) complex one coordination position is occupied by water molecule and another by hydroxy group. Presence of coordinated water molecules, OH⁻ and CH₃COO⁻ groups has been confirmed by IR and elemental analysis. The presence of chloride ion in Cr(III) complex has been confirmed by elemental analysis.

Flufenamic acid complexes were isolated at pH 5-6. On the basis of various physico-chemical investigations it has been found that the drug flufenamic acid behaves as a monoproton bidentate ligand coordinated through nitrogen of >NH group and oxygen of COO⁻ group. The complexes were octahedral having metal and the ligand in the molar ratio 1:2 for Cr(III), Fe(III), Co(II), Ni(II), Cu(II) and Zn(II) and 1:1 for Mn(II). Two/three coordination position are occupied by water molecules but in case of Fe(III) complex of one coordination position is occupied by water molecule and another by hydroxy group. Presence of coordinated water molecules, OH⁻ and CH₃COO⁻ groups were confirmed by IR and elemental analysis. The presence of chloride ion in Cr(III) complex has been confirmed by elemental analysis.

Piroxicam complexes were isolated at pH 5-8. On the basis of various physico-chemical observation it has been found that the drug piroxicam behaves as a monoproton bidentate ligand coordinating through oxygen of
-OH and > C=O groups. The complexes were octahedral with metal ion and ligand in the molar ratio 1 : 2 for Cr(III), Fe(III), Ni(II) and Zn(II) and 1 : 1 for Mn(II), Co(II) and Cu(II). Two/three coordination position are occupied by water molecules while but in case of Fe(III) complex one coordination position is occupied water molecule and another by hydroxy group. Presence of coordinated water molecules, OH· and CH₃COO· groups were confirmed by IR and elemental analysis. The presence of chloride ion in Cr(III) complex has been confirmed by elemental analysis.

CHAPTER - V

This chapter deals with general introduction of pharmacology, general description of the antiinflammatory activity and techniques of the evaluation of antiinflammatory activity.

Antiinflammatory activity of the drugs diclofenac sodium, mefenamic acid, flufenamic acid, piroxicam and its complexes has been tested by adopting the carrageenan induced rat paw edema method using diclofenac sodium, mefenamic acid, flufenamic acid and piroxicam as standard in the respective cases.

Antiinflammatory activity of the complexes were performed using a plethysmometer to measure carrageenan induced rat paw volume following the method of Winter et al. It has been observed that the dose 100 mg/kg body weight of the Cr(III), and Zn(II) complexes of diclofenac sodium shows higher percent inhibition of edema as compared to parent drug.

It has been found that Cr(III) and Zn(II) complexes of mefenamic acid show higher percent inhibition of edema as compared to parent drug. Cr(III), Mn(II) and Ni(II) complexes of flufenamic acid show higher percent inhibition of edema as compared to parent drug. Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II) and Zn(II) complexes of piroxicam show higher percent inhibition of edema as compared to parent drug. These results provide an
evidence for a unique metabolite, metal-dependant metabolic process required for tissue maintenance. A metal coordination compounds which may be responsible for the desired antiinflammatory activity of those agents which have clinical usefulness.

More active complexes possibly depressed the synthesis of the proinflammatory (vasodilator) prostaglandin, PGE$_2$ in the carrageenan pouch model of inflammation. This is in consistent with the work of Lee and Lands, and recently confirmed by Moddox, who found a depression in PGE$_2$ synthesis and a concomitant increase in the antiinflammatory (vasoconstrictor) prostaglandin, PGF$_{2\alpha}$, following the addition of copper sulphate or chloride to seminal vesicle homogenates. These results suggest that the mechanism action of effective complexes may be, at least in part, at the level of the prostaglandin mediation of inflammation. This is to say, these complexes may play a role in decreasing the synthesis of the proinflammatory PGE$_2$ and concomitantly, increasing the synthesis of the antiinflammatory PGF$_{2\alpha}$. 