4.1 Proton ligand stability constants

The Proton ligand stability constants of all drugs were determined in 20% (v/v) ethanol-water medium in the presence of 0.1M sodium perchlorate at three different temperatures 25 °C, 35 °C and 45 °C. The drug L2 and L5 have only one pKₐ where as L1, L3, L4, L6 and L7 drugs have two pKₐ values. The $n_A$ value ranges between 0.2 to 0.8 indicates the presence of only one pKₐ value, whereas 0.2 to 1.8 range of $n_A$ shows two pKₐ values. The amino group(s), carboxyl or hydroxyl groups are the bonding sites in the present drugs and order of pKₐ values of seven drugs are as follows

$$L_6 > L_4 > L_1 > L_3 > L_7 > L_5 > L_2$$

This indicates that ADO has lowest basicity whereas OTC has highest basicity. The present drugs are in diverse nature, hence it is difficult to correlate pKₐ values of one ligand with others. It is observed that the pKₐ values decreases with increase in temperature and presented in Table 3.5

*Metformin hydrochloride* contains one primary, three secondary and one tertiary –N atom. Out of three secondary amino groups, two are having C=N bond. Hence the electrons present in these N atoms may experience the force of repulsion
due to delocalized π electrons. One secondary amino group is attached to two carbon atoms by single bonds. Hence, it might be expected that protonation may be taking place at the primary NH$_2$ group as well as at =NH group easily, rather than a NH-group. This results in two pK$_a$ values 2.905 and 11.101. The pK$_a$ in the basic range is due to the presence of –NH$_2$, whereas the pK$_a$ in the acidic range might be due to steric hindrance and lesser cases of electron pair from –NH-group. The complex formation capacity of MTF drug is much more due to the presence of one free primary amino group and two terminal =NH group.

**Oxytetracycline hydrochloride** contains four hexacyclic rings. There are six hydroxyl groups attached to different rings, out of six one is phenolic –OH, remaining are cyclic alcoholic –OH groups. The rings also possess two exocyclic carbonyl groups, one tertiary amino group and one amide (CONH$_2$) group. The dimethyl ammonium group has been considered to be the most basic functional group of tetracyclines, therefore the metal can be attached either to the tricarbonyl-methan or the phenol-diketone areas. The OTC under experimental conditions shows only one protonation constant that too in the acidic range. Instead of the hydroxyl groups and carbonyl groups, nitrogen of amide or tertiary amino group might be involved in the protonation. The possibility of ternary group is ruled out due to steric hindrance. Moreover, the pK$_a$ value (4.316) is close to the amide group. Hence deprotonation-protonation equilibria might be taking place at amide groups only.

**Cefotaxime sodium consists** of ester group, N and S containing heterocyclic rings, NH-CO group, N-OCH$_3$ groups along with –COO and NH$_2$. As it has been an established fact that carboxylate and amino groups are most promising
coordinating groups. Hence, in the present investigation two pKₐ values, 3.156 corresponding to –COO- and 10.764 corresponding to amino group are obtained. The pKₐ for carboxylic group represents its acidic character whereas basic pKₐ indicate the deprotonation of –N⁺H₃. The dissociation of a third proton from –CONH group is beyond the pH-metric titration range. Since in the measurable range only two pKₐ values are obtained, indicating that CFO has two fully protonated form.

**Ceftriaxone Sodium** drug shows two pKₐ values. Since carboxylate and amino groups are most promising co-ordinating groups, the pK₁ (4.093) value corresponding to –COO- and pK₂ (10.741) value corresponding to amino group are obtained. The pKₐ for carboxylic group represents its acidic character whereas basic pKₐ indicate the deprotonation of –N⁺H₃. The CFT under experimental conditions shows only two protonation constant, indicating that deprotonation of other groups does not take place.

**Imipramine hydrochloride** drug shows only one pKₐ value. The protonation constant for IMP obtained under the experimental condition is 9.062. This is due to the presence of two ternary amine nitrogen. Out of these two, the terminal of the tertiary amino group might have been involved in the complexation. The dimethyl ammonium group is considered to be the most basic functional group of any ligand².

**Adenosine** has N-atom as the binding site. The functional group NH₂ is mostly responsible for complexation, although there are nitrogen atoms present in the coordinate bond formation. Adenosine contains three OH groups, out of these two are attached to cyclic ring and one is to the side chain. The deprotonation of
side chain –OH is easier compared to –OH directly attached to the ring. Hence only one deprotonation in the acidic range (3.292) and the other pK\textsubscript{a} in the basic region correspond to –NH\textsubscript{2} group only (11.659).

*Isoniazid* drug shows two pK\textsubscript{a} values due to two dissociable protons\textsuperscript{3}. The pK\textsubscript{1} (3.192) value can be assigned to the substituted amide (-CONHR) group which is near to the pK\textsubscript{a} value of nicotinamide. The low value of pK\textsubscript{1} may be attributed to the weak basic nature of amide group. The pK\textsubscript{2} (10.657) value is assigned to the (R-NH-NH\textsubscript{2}) group which is attributed to the deprotonation of primary amino group\textsuperscript{3}.

The values of pK\textsubscript{a} of all drugs obtained by half integral method and pointwise calculation method are found to be in good agreement with each other and literature values.

### 4.2 Metal ligand stability constants of transition metal complexes

The calculated values of logK\textsubscript{1}, logK\textsubscript{2} and logβ of drug complexes with transition metal ions Fe(III), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) are presented in Table 3.9A, B to 3.11A, B. The considerable deviation along the volume axis of the metal complex titration curve from ligand titration curve is an indication of chelation in solution. In all the systems studied, the deviation of the metal titration curve from ligand titration curve lies in the region where hydrolysis is not expected and so chelation takes place.

The influence of various factors on the stability constants of metal complexes studied is discussed below.
4.3 Effect of ligand basicity

The metal ions and hydrogen ions act as Lewis acids. The interaction of metal ion with a base is similar to the neutralization reaction involving hydrogen ion. It is assumed that the ionic and coulombic forces responsible for binding a proton should be the same as those responsible for binding the metal ion in a chelate, provided steric and resonance effect in the ligand remains unaltered. On this basis formal analogy between metal ligand and the proton-base system has been developed by J. Bjerrum\textsuperscript{4}, who pointed out that the bases which have the strongest affinity for hydrogen ions form more stable complexes. In general, it may be expected that the more basic ligands form more stable complexes. It is reasonable, therefore, to expect that there should be a similarity in the factors influencing the bonding of hydrogen ion and metal ions to Lewis base. J. Bjerrum, in his study of silver complexes with various amines showed a relationship between $\log K_{Ag^+}$ and $\log K_{H^+}$ for the ligands. The similar linear relationship was shown by several workers\textsuperscript{5-14} between the logK of a series of metal complexes derived from one metal ion with a set of similar ligands and their pKa values.

Calvin and Wilson’s\textsuperscript{15} measurements on the stability constants of the complexes of diketones and hydroxy aldehydes with copper (II) show a similarity between the strength of the L- Cu$^{2+}$ and L- H$^+$ bonds. In all cases logK\textsubscript{1} and logK\textsubscript{2} were obtained for copper complexes and $K_1 > K_2$ as required by statistical effect. On plotting the average value of logK\textsubscript{av} against logK\textsubscript{H+} they concluded that at least two factors influence the strength of the metal ligand bonds. The first includes the effects of charge and charge distribution in the ligand and the charge and size of the cation. The second is attributed to the double bond character of the bond between the metal and the ligand. The coordinate bond between metal containing
d-electrons and an atom containing a vacant d-orbital of sufficiently low energy always has a certain amount of double bond character. This is due to the tendency of metal to share these electrons with the atoms, which donates an electron pair to it to form the coordinate bond.

The general form of the equation \( \log K = a \, \text{pK} + b \) was first proved by Bjerrum. Exceptions to this rule occur in cases where stereochemical considerations show that the ligand molecules will, for one reason or another not get well around the metal ions. There are evidences that the above relation does not hold in the same series of ligands.

Calvin and Wilson\textsuperscript{15} found, but did not comment on the fact that, although there was a rough linear relation between \( \text{pK} \) and \( \log K \), many salicylaldehyde derivatives give results deviating strongly from it. For 8-hydroxy-quinoline, use of only one acidic dissociation constant \( (\text{pK}_{\text{on}}) \) did cause the linear relation\textsuperscript{12}. A rough linear relation was found between \( \text{pK} \) and \( \log K \) for certain types of substituents such as -CH\textsubscript{3}, Cl and -NO\textsubscript{2} groups in salicylaldehyde\textsuperscript{16}, number of workers stressed that the linear relation fails if the conjugated system of the ligand extended through carbon chain e.g. Phenyl substituent in acetyl acetone\textsuperscript{16}. It is supposed that a substituent such as a nitro group interacts with a conjugated hydrocarbon in much the same way as an extension of the conjugation; there should thus be changes in both \( \sigma^- \) and \( \pi^- \) electron densities throughout the molecule. Such changes may alter the stability of HL in a manner different from that of ML.

The validity of linear relation has been examined for the present complexes by plotting \( \text{pK}_1 \) vs \( \log K_1 \). No linearity could be obtained except in some cases, which were expected in the light of the above discussion. The ionization potential of the metal ion and donor atoms, tendency of metal ions to form \( \pi^- \) bonds, ligand
field stabilization of ligand is some of the factors which affect the linear relationship. The linear relationship depends considerably on the nature of ligands.\(^\text{17}\)

The direct correlation of stabilities of metal complexes with ligand basicities is based on the assumption that the base strength is a measure of the \(\sigma^*\) bonding ability of ligands with metal ions. Since the basicities of the present ligands are not of the same order, these correlations would not throw any light on the steric and \(\pi^*\) interactions in the metal ligand system.\(^\text{18}\) This can be achieved by a comparison of the stability per unit base strength defined as the ratio of stability constants to the total basic strength of the ligand i.e. \(\frac{\log \beta}{\sum pK}\) for various metal complexes.\(^\text{18-20}\) These ratios for the present complexes are presented in Table 4.1. The significantly greater values of trivalent Fe(III) complexes indicate the extensive \(\pi^*\) interactions in iron chelates.

**Table 4.1 Stability constant per unit base strength for various metal-ligand systems** \((\log \beta / \sum pK)\) at temperature 25 ± 0.1 °C

<table>
<thead>
<tr>
<th><strong>Metal ion</strong></th>
<th>(L_1)</th>
<th>(L_2)</th>
<th>(L_3)</th>
<th>(L_4)</th>
<th>(L_5)</th>
<th>(L_6)</th>
<th>(L_7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe(III)</td>
<td>1.59</td>
<td>2.28</td>
<td>1.62</td>
<td>--</td>
<td>2.07</td>
<td>1.52</td>
<td>1.63</td>
</tr>
<tr>
<td>Co(II)</td>
<td>0.68</td>
<td>1.57</td>
<td>0.75</td>
<td>0.60</td>
<td>0.71</td>
<td>0.72</td>
<td>0.71</td>
</tr>
<tr>
<td>Ni(II)</td>
<td>0.72</td>
<td>1.83</td>
<td>0.93</td>
<td>0.66</td>
<td>0.72</td>
<td>0.74</td>
<td>0.74</td>
</tr>
<tr>
<td>Cu(II)</td>
<td>1.06</td>
<td>2.14</td>
<td>1.22</td>
<td>0.89</td>
<td>1.18</td>
<td>1.10</td>
<td>1.19</td>
</tr>
<tr>
<td>Zn(II)</td>
<td>0.83</td>
<td>1.65</td>
<td>0.86</td>
<td>0.67</td>
<td>0.88</td>
<td>0.90</td>
<td>0.78</td>
</tr>
<tr>
<td>Cd(II)</td>
<td>0.70</td>
<td>1.32</td>
<td>0.84</td>
<td>0.63</td>
<td>1.03</td>
<td>0.70</td>
<td>0.69</td>
</tr>
</tbody>
</table>
4.4 Effect of metal ions

It is known that the stabilities of the complexes of particular ligands vary with the position of the metal in the periodic table, of course, being a function of the electronic structure of the metal.

Mellor and Maley\textsuperscript{21} reported the stability order of salicylaldehyde-metal complexes as

\[
Pd > Cu > Ni > Pb > Co > Zn > Cd > Mg.
\]

In every case \( K_1 > K_2 \) and no abnormal effects were found. The same workers later\textsuperscript{22} showed that a similar order is obtained for the complexes of pyridine and ethylene diamine.

Karala et al.\textsuperscript{23} studied the 2-amino-3-hydroxy pyridine complexes of some bivalent metal ions and showed that the complexes follows the order as:

\[
\text{Cu(II)} > \text{Zn(II)} > \text{Ni(II)} > \text{Co(II)} > \text{Cd(II)}
\]

The order of stability constants of the complexes of some bivalent metals with some schiffs bases was reported by Mayadeo et al.\textsuperscript{24} as

\[
\text{Co(II)} < \text{Ni(II)} < \text{Cu(II)} > \text{Zn(II)}
\]

The order of stability \( \text{Cu} > \text{Ni} > \text{Co} > \text{Zn} \) was reported for the transition metal complexes with 2-hydrozy-1-naphaldehyde thiosemicarbazone in dioxane water medium\textsuperscript{25}.

Irving and Williams\textsuperscript{26} reported the relation between atomic number of the metal ions and their stability constants. They plotted \( \log K_n \) against the atomic number of the metal ions from Mn(II) to Zn(II) and showed that the stability increases with the increase in atomic number up to the end of transitional series and then decreases again at zinc. The order of stability was
**Mn < Fe < Co < Ni < Cu > Zn**

unless special factors such as steric hindrance, which depends only on ionic size and the spatial arrangement of bonds are operative above order is found for all ligands. The explanation of this regularity must be that the metal ligand bond strength depends on the metal to a considerable extent, since it does not matter whether the metal atom is attached to oxygen, nitrogen or sulphur. The reason for the increase of bond strength with rise of atomic number is not yet clear, but fall from copper to zinc can be explained. In cupric compounds d-orbitals are available for bond formation whereas in zinc complexes no d-orbital of low energy are vacant.

Calvin and Melchior\textsuperscript{27} attempted to explain the phenomenon by comparing the number of properties of the ions under discussion such as the ionic radius, heat of hydration, partial molar entropy and ionization potentials. The only obvious correlation was between stability and the second ionization potentials of the elements. The authors pointed out that except for zinc, this potential measure the energy required for removal of d-electron and they suggest that co-ordination replaces this electron, so that in each case (except Zn), the hybridization should involve d-orbital.

Sahadev et al.\textsuperscript{28} reported the order of metal complexes of 2-hydroxy-1-naphthaldehyde monosemicarbazone as

\[ \text{Cu} > \text{Ni} > \text{Co} > \text{Zn} > \text{Pb} > \text{Cd} > \text{Mn} > \text{Mg} \]

Which was in good agreement with Mellor and Maley.

In order to test the validity of above observations the logβ values obtained in the present investigation for Fe(III), Cu(II), Ni(II), Co(II), Zn(II) and Cd(III) were plotted against the atomic number of metal ions **Figure 3.14.**
It is clear from the figure that the seven ligands follow the following order of stability of their complexes

\[ L_1: Fe^{3+} > Cu^{2+} > Zn^{2+} > Ni^{2+} > Cd^{2+} > Co^{2+} \]

\[ L_2: Fe^{3+} > Cu^{2+} > Ni^{2+} > Zn^{2+} > Co^{3+} > Cd^{2+} \]

\[ L_3: Fe^{3+} > Cu^{2+} > Ni^{2+} > Zn^{2+} > Cd^{2+} > Co^{3+} \]

\[ L_4: Cu^{2+} > Zn^{2+} > Ni^{2+} > Cd^{2+} > Co^{2+} \]

\[ L_5: Fe^{3+} > Cu^{2+} > Zn^{2+} > Ni^{2+} > Cd^{2+} > Co^{2+} \]

\[ L_6: Fe^{3+} > Cu^{2+} > Zn^{2+} > Ni^{2+} > Co^{2+} > Cd^{2+} \]

\[ L_7: Fe^{3+} > Cu^{2+} > Zn^{2+} > Ni^{2+} > Co^{2+} > Cd^{2+} \]

The above stabilities of metal complexes with all ligands are similar to the observations made by the several research workers\(^{21, 22, 29-43}\) and are in accordance with the Irving and Williams order.

**4.5 The chelate effect**

The ligand effect is classified into the electrostatic effect and rest effect. The electrostatic effect represents the effect of any ionic charge on the ligand. This shows the effect of coordination of a charged ion on the already charged species of the complex. The magnitude of the electrostatic effect is related to the work done to bring an electrically charged ligand L to a complex ML\(_n\) to give ML\(_{n+1}\). By considering the electronic charge, dielectric constant of the medium and distance between charges the complex can be determined. The rest effect shows that the ligand molecule affects the ability of further ligand molecules to attach themselves to the lower complex already formed.
The bidentate ligands first attach itself to one coordination position and then second coordinating site forms bond with second position. Therefore $\log K_1$ values of metal complexes are found greater than $\log K_2$. The synthesis of cobalt complexes with ammonia (monodentate) and ethylene diamine (bidentate) ligands suggested that the bidentate ligands forms more stable complexes than monodentate ligands$^{44}$. In solution, at equilibrium during the dissociation process of complexes, ammonia molecules dissociate freely from metal ions where as ethylene diamine detach from one coordinating site and other group holds it in the vicinity of that metal ions hence readily attaches than monodentate.

The origin of the chelate effect has been analyzed by Schwarzenbac$^{45}$ and Adamson$^{46}$ in their separate models. Adamson's approach seems to be simpler. This approach requires no assumptions about ligand geometry or the length of the bridge connecting two or more donor atoms and represented by equation as

$$\log K_1 (\text{bidentate}) = \log K_1 (\text{unidentate}) + \log (55.5)$$

The log (55.5) represents the entropy of translation of one mole of solute generated at one molar concentration and its utility of this equation has been shown by Hancock and Martell$^{47}$ for several metal chelates. The present metal complexes show agreement with the above discussion and suggests that chelate effect is valid for chelates formed by the ligands.

In the present investigation ligand Ceftriaxone Sodium ($L_4$) drug forms orange color precipitate immediately after addition of Iron(III) metal ion solution at pH close to 2.0. Therefore, its complication study was terminated.
4.6 Effect of temperature

The quantitative measure of the stability is expressed in terms of Gibbs free energy changes $\Delta G$ of chelation. The change in free energy is directly related to the logK values. The $\Delta G$ cannot always be used as a diagnostic of the type of ion association reactions taking place, without the knowledge of enthalpy and entropy changes. To interpret the relative stabilities of proton-ligand and metal-ligand complexes, it is necessary to know the changes in free energy, entropy and enthalpy. Deviation from a linear relationship between logK and pK may arise from enthalpy considerations. Enthalpy changes are mainly due to the difference in electron density of the donor atoms, whereas entropy changes are influenced by $\pi$-bonding between the metal ion and the ligand and by steric hindrance. The entropy is related with the change of particles in the system and with the various modes of motion of molecules and atoms. The above factors are related to the forces acting between the ions and the water molecules in the hydration sphere and the forces between metal ions and ligands.

In order to evaluate this, the stability constants of transition metal complexes with drugs in 20% (v/v) ethanol-water medium has been determined at three different temperatures 25 $^\circ$C, 35 $^\circ$C and 45 $^\circ$C, the stability constant data are shown in Table 3.9A, B to 3.11A, B.

The thermodynamic parameter such as change in Gibb’s free energy ($\Delta G$) of the ligands is calculated by using the following equation.

$$\Delta G = -2.303 RT \log K$$
Where \( R \) (ideal gas constant) = \( 8.314 \, \text{JK}^{-1} \text{mol}^{-1} \)

\( K \) is the dissociation constant for the ligand or the stability constant of the complex and \( T \) is absolute temperature in Kelvin (K)

The change in enthalpy (\( \Delta H \)) is calculated by plotting \( \log K \) vs \( \frac{1}{T} \)

The equation utilized for the calculation of changes in enthalpy is as

\[
\text{Slope} = -\frac{\Delta H}{2.303R}
\]

The evaluation of changes in entropy (\( \Delta S \)) is done by the following equation.

\[
\Delta S = \frac{(\Delta H - \Delta G)}{T}
\]

The data obtained for the determination of change in Gibb’s free energy (\( \Delta G \)), change in enthalpy (\( \Delta H \)) and changes in entropy (\( \Delta S \)) for drugs L₁ to L₇ are presented in Table 3.12A, B, C to 3.18A, B, C. The stability constant values of the complexes decrease with the increase in temperature which indicates that high temperature does not favor for the formation of the stable complexes. The values incorporated in the tabular form indicates that the change in enthalpy and entropy of the chelates of the metal ions with the same ligands do not show any regularity, which is in accordance with the Basolo and Pearson order\(^{29}\).

The proton-ligand stability constant (pK\(_a\)) values decreases with increase in temperature for all systems i.e. the acidity of the ligand increases\(^{48}\). This suggested that the liberation of protons becomes easier at higher temperature. The values of
metal-ligand stability constant decreases with increase in temperature. This suggests that the complex formation is exothermic and favorable at lower temperature. The tables show that the $\Delta G$ values had no sharp behavior with temperature, indicating the independent nature of the reactions with respect to temperature\(^{49}\).

The negative value of $\Delta G_1$ and $\Delta G_2$ indicates that the formation of 1:1 and 1:2 metal-ligand complexes in all the cases are thermodynamically favored processes and stable complex is formed. The negative value of $\Delta H_1$ and $\Delta H_2$ show that these reactions are exothermic in nature\(^{50}\).

The negative values of $\Delta H$ and $\Delta G$ of complex formation indicate that the complex formation process is spontaneous\(^{51}\). All the metal complexes are accompanied by negative enthalpy ($\Delta H$) changes suggesting that the metal-ligand bonds are fairly strong. Positive entropy changes accompanying a given reaction are due to the release of bound water molecules from the metal chelates. During the formation of metal chelates, water molecules from the primary hydration sphere of the metal ion are displaced by the chelating ligand. Thus there is an increase in the number of particles in the system i.e. randomness of the system increases\(^{52}\).

The positive value of $\Delta S$ is considered to be the principal driving force for the formation of respective complex species. More positive values of $\Delta S$ may result due to an increase in the number of particles after the reaction and is responsible for giving more negative values of $\Delta G$\(^{53}\).
According to Martell and Calvin\textsuperscript{54} positive entropy effects was predicted towards an increase in the number of particles after the reaction. This positive $\Delta S$ is responsible to give more negative $\Delta G$.

The high positive values of $\Delta S_1$ and $\Delta S_2$ in some cases indicate that the entropy effect is predominant over enthalpy effect. The positive $\Delta S$ values for some metal complexes indicated that the formation of these complexes was entropy favored, while negative $\Delta S$ values for some metal complexes suggesting a highly solvated metal complexes\textsuperscript{49}.

The result obtained in the present investigation is in good agreement with the many researchers\textsuperscript{48-50, 55-64} and their observations on metal chelates involving biologically active ligands.
Part-II: Rare earth metals (Lanthanides)

4.7 Metal ligand stability constants of rare earth metal complexes

The calculated values of $\log K_1$, $\log K_2$ and $\log \beta$ of drug complexes with lanthanide metal ions La(III), Ce(III), Nd(III), Sm(III), Gd(III), Tb(III) and Dy(III) at three different temperatures 25 ºC, 35 ºC and 45 ºC are presented in Tables 3.26A, B to 3.28A, B. The considerable deviation along the volume axis of the metal complex titration curve from ligand titration curve is an indication of chelation in solution. In all the systems studied, the deviation of the metal titration curve from ligand titration curve lies in the region where hydrolysis is not expected and so chelation takes place.

Due to the shielding of f-electrons, lanthanide form mostly ionic compounds. If bonds in the lanthanide compounds are ionic, the following relationship given by the Born for energy change on complexation of a gaseous ion charge ‘e’ and radius ‘r’ in a medium of dielectric constant ‘D’ as

$$ E = \frac{e^2}{2r} \left[ 1 - \frac{1}{D} \right] $$

Since, the stability constants are related directly to this energy, it is expected that the logK values for various rare earths should increase linearly with $e^2/r$. Such a relationship has been tested for a number of rare earth complexes.$^{65-68}$

Moeller et al.$^{65}$ observed the regular increase in stabilities with increase in atomic number (i.e. with decrease in ionic radius) from La to Sm and there is,
however, a discontinuity at Gd (gadolinium break). For the ions beyond gadolinium two distinct types of behaviors have been observed.

1. A normal increase in stability with decrease in radius in the complexes of EDTA and NTA.

2. An essential constancy or occasional maxima or minima in the plot of logK vs $e^2/2r$ in the complexes of IMDA, HEDTA and DTPA$^{69-71}$.

The shielding of 4f electrons is exhibited in the stability constants of the present rare earth metal complexes with medicinal drugs reported in Tables 3.26A, B to 3.28A, B. Which show that there is very little difference in these values with the increase in the atomic number. The order of stability constants of the complexes with respect to metal ions with all the ligands observed is as follows.

$$\text{La} < \text{Ce} < \text{Nd} < \text{Sm} > \text{Gd} < \text{Tb} < \text{Dy}$$

In the present complexes the rare earth metal ions bind predominantly to oxygen and weakly to nitrogen in drugs$^{72}$. The plot of log$\beta$ vs atomic number (Figure3.28) and log$\beta$ vs 1/r (Figure3.29) for these complexes shows a regular increase of stability constants from La (III) to Sm (III) with a discontinuity at gadolinium, which is commonly known as ‘gadolinium break’. After gadolinium, the values of stability constants increase up to dysprosium.

The gadolinium break observed in all the complexes may be correlated to discontinuity in crystal radia of gadolinium. In all the cases Gd(III) complexes have lower values of logK as compared to those of Sm(III) and Tb(III) complexes. As we proceed through the lanthanide series, the nuclear charge and the number of
4f electrons increases by one at each step. The shielding of 4f electrons from the 
other is quite imperfect owing to the shifts of orbits, so that, at each increase the 
effective nuclear charge experienced by each 4f electrons increased, thus causing a 
reduction in the size of the entire 4f shell. The lowering in logβ values in Gd(III) 
chelates in relation with the corresponding Sm(III) and Tb(III) chelates may be 
due to fact that progressively smaller radia impose hindrance on the ligands on 
account of metal-ligand interactions.

The relationship logK = a pK + b, was used to understand the effect of 
substituent groups on the chelating tendencies of ligands. The stability per unit 
base strength defined as the ratio of stability constants to the total basic strength of 
the ligand i.e. \( \frac{\log\beta}{\sum pK} \) for various metal complexes. These ratios for the present 
complexes are presented in Table 4.2. The basicities of the present ligands are not 
of the same order which may be attributed to a metal ligand system where there are 
no effect on the steric and \( \pi \) interactions and \( \sigma \) bonding ability of ligands with 
metal ions also measures the basicity.

Table 4.2 Stability constant per unit base strength for various metal-ligand 
systems (logβ / Σ pK) at temperature 25 ± 0.1 °C

<table>
<thead>
<tr>
<th>Metal ion</th>
<th>( L_1 )</th>
<th>( L_2 )</th>
<th>( L_3 )</th>
<th>( L_4 )</th>
<th>( L_5 )</th>
<th>( L_6 )</th>
<th>( L_7 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>La(III)</td>
<td>0.87</td>
<td>1.78</td>
<td>0.90</td>
<td>0.57</td>
<td>0.95</td>
<td>0.74</td>
<td>0.82</td>
</tr>
<tr>
<td>Ce(III)</td>
<td>0.99</td>
<td>1.82</td>
<td>0.98</td>
<td>0.60</td>
<td>0.99</td>
<td>0.82</td>
<td>0.85</td>
</tr>
<tr>
<td>Nd(III)</td>
<td>1.00</td>
<td>1.91</td>
<td>1.07</td>
<td>0.61</td>
<td>1.14</td>
<td>0.87</td>
<td>0.93</td>
</tr>
<tr>
<td>Sm(III)</td>
<td>1.01</td>
<td>1.99</td>
<td>1.12</td>
<td>0.71</td>
<td>1.17</td>
<td>0.99</td>
<td>1.04</td>
</tr>
<tr>
<td>Gd(III)</td>
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<td>1.93</td>
<td>0.97</td>
<td>0.69</td>
<td>1.02</td>
<td>0.96</td>
<td>0.91</td>
</tr>
<tr>
<td>Tb(III)</td>
<td>1.04</td>
<td>2.01</td>
<td>1.02</td>
<td>0.70</td>
<td>1.12</td>
<td>1.02</td>
<td>1.01</td>
</tr>
<tr>
<td>Dy(III)</td>
<td>1.07</td>
<td>2.05</td>
<td>1.11</td>
<td>0.72</td>
<td>1.14</td>
<td>1.04</td>
<td>1.03</td>
</tr>
</tbody>
</table>
4.8 Relation between thermodynamic functions and stability constants

Knowledge of enthalpy and entropy for complex formation of rare earths enable us to interpret the trends in logK values of complexes in solution. The enthalpy change is assumed to depend mainly on the difference in bond energy between the coordinated water and the ligand. The entropy is concerned with the various modes of motions of molecules and atoms with restriction on their movement and also with a change in the number of particles in the system. These factors are concerned with the forces acting between the ions and water molecules in the hydration shell and the forces between the ions and the ligands i.e with the factors determining the enthalpy changes accompanying complex formation.

A large number of investigations of thermodynamic properties of various rare earth metal complexes have been published\textsuperscript{70-79}. In their observations, considerable disagreement was found in the interpretation of ΔH and ΔS values. To explain this, Frank et al.\textsuperscript{80} and Gurney\textsuperscript{81} proposed a model of ionic solutions, which considers three concentric zones of water about each ion, the innermost consists of one or more layers of water molecules oriented by ionic interaction. The outermost zone has the hydrogen bonded structure of normal water, the middle zone of less order than bulk solution phase.

Choppin et al.\textsuperscript{82, 83} showed that lanthanides have a larger inner zone and small middle zone. The change in enthalpy (ΔH) and change in entropy (ΔS) in complex formation will reflect the knowledge of disruption of this solvent structure as well as a combination of ions. They also reported that in the inner sphere
complexes the hydration zone is disrupted to a greater extent and elimination of water molecules from the inner hydration zone to the middle.

In the present study the thermodynamic parameters for lanthanide complexes with drugs were obtained from the data of logK₁ and logK₂ at three different temperatures 25 °C, 35 °C and 45 °C by using the same methods used for transition metal complexes. The values of Gibb’s free energy change (ΔG), entropy change (ΔS) and enthalpy change (ΔH) at three different temperatures 25 °C, 35 °C and 45 °C are listed in Table 3.29A, B, C to 3.35A, B, C. It could be seen from the tables that the logK₁ and logK₂ values decreases with the increase in temperature indicating that the high temperature does not favor the formation of stable complexes.

The negative ΔG values indicate that both dissociation of the ligand and the complexation process are spontaneous. These values have no sharp behavior with temperature showing the independent nature of the reactions with respect to temperature. The more negative values of ΔG₁ than ΔG₂ indicate that the 1:1 complexes formation is energetically favored. The negative values of ΔH for the complexation show that all the complexation reactions are exothermic and the metal-ligand binding process is enthalpy driven.

The positive values of ΔS suggest a desolvation of the ligands, resulting in weak solvent-ligand interactions, to the advantage of the metal ion-ligand interaction. Also the negative values of ΔS are pointing to increased ordering due to association. The results obtained in the present investigation are in good agreement with the several researchers.
Part-III: Ternary complexes

4.9 Formation of ternary complexes

The formation of ternary (mixed ligand) complexes has been confirmed by the non superimposable nature of composite curve\textsuperscript{90} on the experimental mixed ligand curve. The theoretical composite curve ‘C’ remains towards the left of the mixed ligand curve indicates the formation of ternary complexes and interaction between ML and R to form MLR ternary complexation.

The representative zinc and cobalt mixed ligand titration curve systems of Oxytetracycline hydrochloride drug with amino acid DL-Isoleucine (R\textsubscript{4}) and Glycine (R\textsubscript{1}) respectively are shown in Figures 3.30 to 3.31. The decrease in pH occurs when a solution of L or R added to 1:1 primary complex solution of ML or MR which suggest that the release of proton takes place due to mixed ligand complexation and ternary curve lies below the pure ligand curves as well as binary curves indicating the formation of 1:1:1 ternary complex species. If mixed ligand curve does not coincide with either of simple binary curves (ML or MR) confirms the involvement of simultaneous equilibria in the solution otherwise stepwise equilibria\textsuperscript{91-93}. The nature of mixed ligand titration curves indicates that complex formation takes place in the pH range of 2.5 to 6.0 in the representative systems.

In other many systems complex formation takes place in the pH range of 3.0 to 8.0. It was also observed that the mixed ligand titration curve coincides with 1:1 titration curve at the lower pH region and deviates at the higher pH region from which secondary ligand starts coordinating with ML or MR species to form ternary chelate MLR or MRL and there is no any solid phase formed during the course of titrations.
4.10 Stability of ternary complex systems

Ternary (mixed ligand) complexes of Zn(II) and Co(II) transition metal ions with seven drugs and eight amino acids (i.e. One hundred and twelve systems) were studied and their stability constants along with some relative parameters were calculated by using ‘SCOGS’ computer programme and the values obtained are enlisted in Table 3.37 to 3.79. The stability of mixed ligand complexes is measured in terms of various parameters like K_L, K_R, K_r and ΔlogK values which explain the variation in the stability constants and the relationship between binary and ternary complexes as given in the following equation

$$K_r = \frac{\beta_{111}^2}{\beta_{20}\cdot\beta_{02}}$$

The change in the stability of the ternary complexes as compared to their binary analogues is based on above equation. This corresponds to the equilibrium as

$$ML_2 + MR_2 \rightleftharpoons 2MLR$$

Watters et al. and Kida calculated the statistically expected value of K_r (0.6) by considering the probabilities of finding the metal ions with the ligands. The stability of ternary complexes is affected by the nature of both primary and secondary ligand. The ligand which first bound to metal ion can influence the bonding property of second ligand to be bounded and stabilization of ternary complex can be governed by the bonding property of secondary ligands because of these more stable ternary complexes has strong bonding with secondary ligand. In addition to K_r, two more constants K_L and K_R are used to discuss the relative stability of mixed ligand and binary complexes. The K_L parameter gives relative stability of ternary complexes with 1:1 stability of primary ligand complexes ML if L is the primary ligand as
\[ K_L = \frac{\beta_{111}}{K_{10}} \]

The positive \( K_L \) accounts for the extra stability of ternary complexes over the stability of ML binary complexes. The \( K_R \) values give changes in the stability of ternary complexes and MR binary complexes if \( R \) is the secondary legend as

\[ K_R = \frac{\beta_{111}}{K_{01}} \]

The \( \Delta \log K \) parameter gives relative stability of ternary complexes and can be calculated by the expression as

\[ \Delta \log K = \log \beta_{111} - [\log K_{10} + \log K_{01}] \]

This indicates that both ligands in the ternary system influence mutually to the same extent. They may be either stabilized or destabilized in their coordination to a particular metal ion. The additional coordination sites of multivalent hydrated metal ions are available to bind for first ligand than second during ternary complexation as suggested by electrostatic theory of binary complex formation (statistical effect) which indicates that \( \Delta \log K \) should be negative due to the usual order \((\beta_{20} > \beta_{11})\) of stability, however there are several exceptions. The negative values of \( \Delta \log K \) suggest that secondary ligand forms more stable complex with hydrated metal ion than ML species. The N-donors like ethylene diamine and amino acids with N and O coordination sites show negative \( \Delta \log K \) values. The higher negative values than statistical values (-0.4) found in some system indicates relatively less stable complexes with the square planar geometry of ternary complexes. The negative value of \( \Delta \log K \) does not mean that the complex is not formed. The negative value may be due to the high stability of its binary complexes, reduced number of coordination sites, steric
hindrance\textsuperscript{108,109}, electronic consideration\textsuperscript{110,111}, difference in bond type, geometrical structure etc. The positive values of $\Delta \log K$ indicate that ternary complex is more favorable and highly stable. The $\Delta \log K$ values of ternary complexes of bipyridyl as a primary ligand are positive for malonic acids, pyrocatechol etc. for O-donors\textsuperscript{101}.

Sigel H.\textsuperscript{105} concluded that in the case of bidentate ligand and amino acid, there are twelve edges of a regular octahedron available to the first entering ligand, but only five for the second. Then the statistical factor would be 5/12 and accordingly $\Delta \log K = -0.4$, -0.6 and -0.9 for square planar and distorted octahedral complexes. Hence the experimentally determined value of $\Delta \log K < -0.6$ indicates less stabilization in ternary complexes. The $\Delta \log K$ value of some system is higher than the statistically expected value, showing the stabilized nature of the ternary complex.

Thomson and Lorass\textsuperscript{92} pointed out that more negative $\Delta \log K$ value of ternary complexes is due to the electrostatic repulsion between the negative charge on the ligand and amino acids. Steric hindrance consideration is the most important factor because in the present studies of ternary complex, primary ligand coordinates with the metal ion in the lower pH range and forms 1:1 and 1:2 complex. In solution, ternary complex forms as the titration curve run below the Zn(II) and Co(II)-drug titration curve. So, it is evident that the entry of the secondary ligand amino acids faces steric hindrance due to bigger size of the Zn(II) and Co(II)-drug complex as compared to aquo ion, which tries to restrict the entry of the secondary ligand in the coordination sphere of the Zn(II) and Co(II) metal ion and thus reduces the stability of ternary complexes.
The perusal of the values of $\log\beta$ of zinc and cobalt metal complexes from Table 3.38 to 3.51 indicates that Zn metal complexes are more stable than Co metal complexes. The order of stability of equilibrium constant $\beta_{111}$ of ternary system ZnLR$_4$ with respect to all primary legend is as:

$$L_1 > L_3 > L_6 > L_4 > L_7 > L_5 > L_2$$

and for ternary system CoLR$_1$ with respect to all primary ligands is as:

$$L_1 > L_4 > L_7 > L_3 > L_6 > L_2 > L_5$$

All the remaining systems do not show similar order of stability. The deviation from this order may be attributed to the nature of secondary ligands. In zinc and cobalt metal complexes of seven drugs and eight amino acids, the Zn(II) complexes shows the maximum number of highest stability constant value, whereas Co(II) shows the maximum number of lowest stability constant value.

The stability constants of ternary systems and related parameters like $K_L$, $K_R$, $K_r$ and $\Delta\log K$ are represented in Table 3.38 to 3.51 and discussed below as the representative system.

**1. Stability of mixed ligand complexes of MTF (L$_1$)**

The Zn(II)L$_1$R$_4$ system shows higher stability constant value (14.00) in the mixed ligand complexes with Metformin hydrochloride drug and eight amino acids whereas Co(II)L$_1$R$_3$ system shows low stability constant value (7.915) as shown in Table 3.38 and 3.39. The order of stability of equilibrium constants $\beta_{111}$ of ternary system of Zn(II) transition metal ion with respect of secondary ligand is as: $R_4 > R_8 > R_1 > R_5 > R_7 > R_6 > R_2 > R_3$ and the order of stability for Co(II) transition metal ion is as: $R_5 > R_8 > R_6 > R_1 > R_2 > R_4 > R_7 > R_3$
II. Stability of mixed ligand complexes of OTC (L₂)

The Zn(II)L₂R₄ system shows relatively higher stability constant value (9.709) in the mixed ligand complexes with Oxytetracycline hydrochloride drug and eight amino acids whereas Co(II)L₂R₂ system shows low stability constant value (6.024) as shown in Table 3.40 and 3.41. The order of stability of equilibrium constants β₁₁₁₁ of ternary system of Zn(II) transition metal ion with respect of secondary ligand is R₄ > R₆ > R₈ > R₅ > R₁ > R₇ > R₂ > R₃ and the order of stability for Co(II) is as R₁ > R₅ > R₆ > R₇ > R₄ > R₇ > R₅ > R₃

III. Stability of mixed ligand complexes of CFO (L₃)

In this system of Cefotaxime sodium drug, Zn(II)L₃R₄ complex shows relatively higher stability constant value (13.287) whereas Co(II)L₃R₂ system shows low stability constant value (8.031) as shown in Table 3.42 and 3.43. The order of stability of equilibrium constants β₁₁₁₁ of ternary system of Zn(II) transition metal ion with respect of secondary ligand is R₄ > R₈ > R₇ > R₁ > R₂ > R₅ > R₆ > R₃ and the order of stability of equilibrium constants β₁₁₁₁ for Co(II) transition metal ion is R₅ > R₄ > R₈ > R₁ > R₆ > R₇ > R₅ > R₃

IV. Stability of mixed ligand complexes of CFT (L₄)

In this system of Ceftriaxone sodium drug, Zn(II)L₄R₄ complex shows high value (11.976) of stability constant whereas Co(II)L₄R₃ system shows minimum value (6.815) of stability constant as shown in Table 3.44 and 3.45. The order of stability of equilibrium constants β₁₁₁₁ of ternary system of Zn(II) transition metal ion with respect of secondary ligand is R₄ > R₈ > R₆ > R₂ > R₅ > R₇ > R₃ and the order of stability of equilibrium constants β₁₁₁₁ for Co(II) transition metal ion is R₁ > R₆ > R₄ > R₇ > R₈ > R₅ > R₆ > R₃
V. Stability of mixed ligand complexes of IMP (L₅)

In this system of Imipramine hydrochloride drug, Zn(II)L₅R₄ complex shows highest value (11.235) of stability constant whereas Co(II)L₅R₃ system shows minimum value (5.72) of stability constant as shown in Table 3.46 and 3.47. The order of stability of equilibrium constants $\beta_{111}$ of ternary system of Zn(II) transition metal ion with respect of secondary ligand is $R₄ > R₁ > R₆ > R₈ > R₂ > R₅ > R₇ > R₃$ and the order of stability for Co(II) transition metal ion with respect of secondary ligand is $R₈ > R₁ > R₅ > R₄ > R₆ > R₂ > R₇ > R₃$

VI. Stability of mixed ligand complexes of ADO (L₆)

The Zn(II)L₆R₄ system shows relatively higher stability constant value (12.903) in the mixed ligand complexes with Adenosine drug and eight amino acids whereas Co(II)L₆R₃ system shows low value (6.591) as shown in Table 3.48 and 3.49. The order of stability of equilibrium constants $\beta_{111}$ of ternary system of Zn(II) transition metal ion with respect of secondary ligand is $R₄ > R₁ > R₆ > R₇ > R₅ > R₂ > R₆ > R₃$ and the order of stability for Co(II) transition metal ion with respect of secondary ligand is as: $R₅ > R₄ > R₆ > R₇ > R₅ > R₁ > R₇ > R₂ > R₃$

VII. Stability of mixed ligand complexes of ISO (L₇)

In this system of isoniazid drug, Zn(II)L₇R₄ complex shows high value (11.60) of stability constant whereas Co(II)L₇R₂ system shows minimum value (8.167) of stability constant as shown in Table 3.50 and 3.51. The order of stability of equilibrium constants $\beta_{111}$ of ternary system of Zn(II) transition metal ion with respect of secondary ligand is $R₄ > R₁ > R₆ > R₇ > R₅ > R₇ > R₂ > R₃$ and the order of stability for Co(II) transition metal ion with respect of secondary ligand is $R₈ > R₆ > R₄ > R₇ > R₅ > R₃ > R₂$
The comparison of equilibrium constants $\beta_{11}$ with $\beta_{20}$ and $\beta_{02}$ of all above mixed ligand systems reveals the preferential formation of ternary complexes over binary complexes\textsuperscript{112}.

All the systems investigated in the present work show the low positive values of $K_L$ and $K_R$ which indicates less stability of ternary complexes with respect to binary complexes of primary as well as secondary ligands and the preferential formation of binary complexes over ternary complexes. The low positive value of $K_r$ indicates lower stability of ternary complexes\textsuperscript{113}. This may be attributed to the interactions outside the coordinating sphere such as formation of hydrogen bonding between coordinated ligands, charge neutralization, chelate effect and electrostatic interactions between non coordinated charge groups of ligands.

The negative values of $\Delta \log K$ have been evaluated in all systems (except ZnL$_5$R$_2$ system), which show the formation of ternary complexes but less stable and destabilized nature of complexes which has been reported in N and O coordination of amino acids\textsuperscript{107}. The higher negative values than statistical values (-0.4) found in some system indicates relatively less stable complexes with the square planar geometry of ternary complexes. The positive value of $\Delta \log K$ have been evaluated only in ZnL$_5$R$_2$ system, which show the formation of more stable ternary complexes.
4.11 Distribution of various complex species with pH

The equilibrium constants of binary and ternary complexes can be calculated for the possible equilibria mentioned above. These constants are not much use unless the distribution of various possible species at different pH values is known. The concentration of total metal, total ligand, free metal, free ligand and various possible species that are formed during the complexation process HL, L, HR, R, ML, MR, ML₂, MR₂ and MLR at different pH were directly obtained as a computer outputs using “SCOGS” computer programme and the representative systems of percentage concentrations of species in zinc and cobalt mixed ligand systems of seven drugs as primary ligands and amino acid R₄(DL-Isoleucine) and R₁(Glycine) as a secondary ligand respectively has been depicted in Table 3.52 to 3.79. The percentage concentrations of these species formed were plotted against the corresponding pH values to obtain species distribution curves and shown in the Figure 3.32 to 3.59. All the graphs were critically analyzed to know the possible equilibria. The formation of mixed ligand complexes of metal (zinc and cobalt) with drugs and amino acid in the present study are as shown below:

\[
ML + R \rightleftharpoons MLR \quad (1)
\]

\[
MR + L \rightleftharpoons MRL \quad (2)
\]

The other way of characterizing these ternary complexes is by disproportion reaction represented by the following equilibrium.

\[
ML₂ + MR₂ \rightleftharpoons 2 MLR
\]
This reaction is possible only if both the ligands form 1:1 and 1:2 complexes individually with the metal ion. The other disproportion reactions are

\[
\begin{align*}
ML_2 + MR & \rightleftharpoons MLR + ML \quad (3) \\
MR_2 + ML & \rightleftharpoons MLR + MR \quad (4) \\
ML + MR & \rightleftharpoons MLR + M \quad (5) \\
M + HL + HR & \rightleftharpoons MLR + 2H \quad (6)
\end{align*}
\]

The equilibrium reactions 4 and 5 corresponds to the systems containing the ligand which forms only 1:1 complex and the other forms both 1:1 and 1:2 complexes. The equilibrium reaction (6) represents the systems containing the ligand which forms only 1:1 binary complexes with the metal ion. This reaction is possible only if the sufficient concentrations of ML and MR are available. The finding of the seven representative systems of zinc and cobalt mixed ligand complexes is discussed below as

I. Zn(II)-MTF(L\textsubscript{1})- Isoleucine (R\textsubscript{4}) & Co(II)-MTF(L\textsubscript{1})-Glycine(R\textsubscript{1}) system

In above systems, primary ligand Metformin hydrochloride and secondary ligands isoleucine and glycine form 1:1 and 1:2 binary complexes with zinc and cobalt. The percentage distribution of free metal, free ligand L and free ligand R and other possible species with the corresponding pH of the system is enlisted in Table 3.52 to 3.55 and percentage distribution curve were drawn by plotting percentage concentration vs pH of these species and are shown in Figure 3.32 to 3.35. The data and figure of percentage distribution of free metal, free ligand L and free ligand R species shows that the percentage concentration of free metal slowly
decreases with increase pH indicates complexation of the metal and the percentage concentration of free ligands L and R increases with increase in pH. This increase in concentration may be due to the dissociation of excess ligands present in the system. All the systems investigated in the present work show similar behavior. The species distribution curve (Table 3.52, Figure 3.32) of ZnL₁R₄ shows that concentrations of free ligand FL (5.53) are more than free ligand FR (3.06) at higher pH (8.6) and the species distribution curve (Table 3.53, Figure 3.33) of CoL₁R₁ species shows that concentrations of free ligand FR (27.89) are more than free ligand FL (22.22) at higher pH (8.8). The species distribution curve of various species of zinc (Table 3.54 and Figure 3.34) shows that the formation of ternary complexes ZnLR is 91.47% at pH 7.6 and the species distribution curve of various species of cobalt (Table 3.55 and Figure 3.35) shows that the formation of ternary complexes CoLR is 50.37% at pH 6.4. The percentage concentrations for the formation of L and HR continuously decreases with increasing pH. The percentage concentrations of ternary complex ZnLR and CoLR species increases with increase in pH, confirm the formation of ternary complexes and possible equilibria in the formation of ternary complex can be expressed by the equation (3) and (4).

II. Zn(II)-OTC(L₂)- Isoleucine (R₄) & Co(II)-OTC(L₂)- Glycine (R₁) system

In these systems primary ligand Oxytetracycline hydrochloride and secondary ligands isoleucine and glycine form 1:1 and 1:2 binary complexes with zinc and cobalt. The percentage distributions of free metal, free ligands L and R and other possible species with the corresponding pH of the system is enlisted in Table 3.56 to 3.60 and percentage distribution curve were drawn by plotting percentage concentration vs pH of these species and are shown in Figure 3.36 to 3.39. The
percentage distribution of free metal, free ligands FL and FR species shows that the percentage concentration of free metal decreases with increase in pH and the percentage concentration of free ligands L and R increases with increase in pH. The species distribution curve (Table 3.56, 3.57 & Figure 3.36, 3.37) for ZnL₂R₄ and CoL₂R₁ species shows that concentrations of free ligand FL are more than free ligand FR at higher pH.

The species distribution curve of various species of zinc (Table 3.58 and Figure 3.38) shows that the formation of ternary complexes ZnLR is 38.27% at pH 7.2 and the species distribution curve of various species of cobalt (Table 3.59 and Figure 3.39) shows that the formation of ternary complexes CoLR is very less 10.50% at pH 7.6. The percentage concentrations for the formation of L and HR continuously decreases with increasing pH. The percentage concentrations of ternary complex Zn and Co species increases with increase in pH, confirm the formation of ternary complexes and possible equilibria in the formation of ternary complex can be expressed by the equation (4)

III. Zn(II)-CFO(L₃)-Isoleucine (R₄) & Co(II)-CFO(L₃)-Glycine (R₄) system

In above systems primary ligand Cefotaxime sodium and secondary ligands isoleucine and glycine forms 1:1 and 1:2 binary complexes with zinc and cobalt. The percentage distribution of free metal, free ligands L and R and other possible species with the corresponding pH of the system is enlisted in Table 3.60 to 3.63 and percentage distribution curve were drawn by plotting percentage concentration vs pH of these species and are shown in Figure 3.40 and 3.41. The table and figure of the percentage distribution of free metal, free ligands FL and FR species shows that the percentage concentration of free metal decreases with increase in
pH and the percentage concentration of free ligands L and R increases with increase in pH.

The species distribution curve (Table 3.60, Figure 3.40) of ZnL₃R₄ shows that concentrations of free ligand FL are more than free ligand FR at higher pH and the species distribution curve (Table 3.61, Figure 3.41) of CoL₃R₁ species shows that concentrations of the free ligand FR are more than free ligand FL at higher pH. The species distribution curve of various species of zinc (Table 3.62 and Figure 3.42) shows that the formation of ternary complexes ZnLR is 90.74% at pH 5.8 and the species distribution curve of various species of cobalt (Table 3.63 and Figure 3.43) shows that the formation of ternary complexes CoLR is 54.69% at pH 7.0. The percentage concentrations for the formation of L and HR continuously decreases with increasing pH. The percentage concentrations of ternary complex ZnLR and CoLR species increases with increase in pH, confirms the formation of ternary complexes and possible equilibria in the formation of ternary complex can be expressed by the equation (4).

IV. Zn(II)-CFT(L₄)-Isoleucine(R₄) & Co(II)-CFT(L₄)-Glycine (R₁) system

In these systems primary ligand Ceftriaxone sodium and secondary ligands isoleucine and glycine forms 1:1 and 1:2 binary complexes with zinc and cobalt. The percentage distribution of free metal, free ligands L and R and other possible species with the corresponding pH of the system is enlisted in Table 3.64 to 3.67 and percentage distribution curve were drawn by plotting percentage concentration vs pH of these species and are shown in Figure 3.44 to 3.47. The percentage distribution of free metal, free ligands FL and FR species shows that the percentage concentration of free metal decreases with increase in pH and the
percentage concentration of free ligands L and R increases with increase in pH. The species distribution curve (Table 3.64, 3.65 & Figure 3.44, 3.45) for ZnL₄R₄ and CoL₄R₁ species shows that concentrations of free ligand FL are more than free ligand FR at higher pH. The species distribution curve of various species of zinc (Table 3.66 and Figure 3.46) shows that the formation of ternary complexes ZnLR is 91.98% at pH 6.4 and the species distribution curve of various species of cobalt (Table 3.67 and Figure 3.47) shows that the formation of ternary complexes CoLR is 49.45% at pH 7.0. The percentage concentrations for the formation of L and HR continuously decreases with increasing pH. The percentage concentrations of ternary complex ZnLR and CoLR species increases with increase in pH, confirms the formation of ternary complexes and possible equilibria in the formation of ternary complex can be expressed by the equation (4)

V. Zn(II)-IMP(L₅)-Isoleucine (R₄) & Co(II)-IMP(L₅)-Glycine (R₁) system

In above systems primary ligand Imipramine hydrochloride and secondary ligands isoleucine and glycine form 1:1 and 1:2 binary complexes with zinc and cobalt. The percentage distribution of free metal, free ligands L and R and other possible species with the corresponding pH of the system is enlisted in Table 3.68 to 3.71 and percentage distribution curve were drawn by plotting percentage concentration vs pH of these species and are shown in Figure 3.48 to 3.51. The percentage distribution of free metal, free ligands FL and FR species shows that the percentage concentration of free metal decreases with increase in pH and the percentage concentration of free ligands L and R increases with increase in pH. The species distribution curve (Table 3.68, 3.69 & Figure 3.48, 3.49) for ZnL₅R₄ and CoL₅R₁ species shows that concentrations of free ligand FL are more than free
ligand FR at higher pH. The species distribution curve of various species of zinc (Table 3.70 and Figure 3.50) shows that the formation of ternary complexes ZnLR is very less 18.61% at higher pH 8.0 and the species distribution curve of various species of cobalt (Table 3.71 and Figure 3.51) shows that the formation of ternary complexes CoLR is also very low 16.43% at higher pH 9.4. The percentage concentrations for the formation of L and HR continuously decreases with increasing pH. The percentage concentrations of ternary complex ZnLR and CoLR species slowly increases with increase in pH, confirms the formation of ternary complexes, but less stable.

VI. Zn(II)-ADO(L₆)-Isoleucine (R₄) & Co(II)-ADO(L₆)-Glycine(R₁) system

In these systems primary ligand Adenosine and secondary ligands isoleucine and glycine form 1:1 and 1:2 binary complexes with zinc and cobalt. The percentage distribution of free metal, free ligands L and R and other possible species with the corresponding pH of the system is enlisted in Table 3.72 to 3.75 and percentage distribution curve were drawn by plotting percentage concentration vs pH of these species and are shown in Figure 3.52 to 3.55. From the data and figure on the percentage distribution of free metal, free ligands FL and FR species it is observed that the percentage concentration of free metal decreases with increase in pH and the percentage concentration of free ligands L and R increases with increase in pH. The species distribution curve (Table 3.72, 3.73 & Figure 3.52, 3.53) for ZnL₆R₄ and CoL₆R₁ species shows that concentrations of the free ligand FR are more than free ligand FL at higher pH. The species distribution curve of various species of zinc (Table 3.74 and Figure 3.54) shows that the formation of ternary complexes ZnLR is very high 94.11% at pH 8.0 and the species
distribution curve of various species of cobalt (Table 3.75 and Figure 3.55) shows that the formation of ternary complexes CoLR is 48.82% at pH 6.2. The percentage concentrations for the formation of L and HR continuously decreases with increasing pH. The percentage concentrations of ternary complex ZnLR and CoLR species increases with increase in pH, confirms the formation of ternary complexes and possible equilibria in the formation of ternary complexes can be expressed by the equation (4).

VII. Zn(II)-ISO(L\textsubscript{7})- Isoleucine (R\textsubscript{4}) & Co(II)-ISO(L\textsubscript{7})-Glycine(R\textsubscript{1}) system

In above systems primary ligand Isoniazid and secondary ligands isoleucine and glycine form 1:1 and 1:2 binary complexes with zinc and cobalt. The percentage distribution of free metal, free ligands L and R and other possible species with the corresponding pH of the system is enlisted in Table 3.76 to 3.79 and percentage distribution curve were drawn by plotting percentage concentration vs pH of these species and are shown in Figure 3.56 to 3.57. The percentage distribution of free metal, free ligands FL and FR species shows that the percentage concentration of free metal decreases with increase in pH and the percentage concentration of free ligands L and R increases with increase in pH. The species distribution curve (Table 3.76, Figure 3.56) of ZnL\textsubscript{7}R\textsubscript{4} shows that concentrations of free ligand FL are more than free ligand FR at higher pH and the species distribution curve (Table 3.77, Figure 3.57) of CoL\textsubscript{7}R\textsubscript{1} species shows that concentrations of the free ligand FR are more than free ligand FL at higher pH. The species distribution curve of various species of zinc (Table 3.78 and Figure 3.58) shows that the formation of ternary complexes ZnLR is 77.95% at pH 6.6 and the species distribution curve of various species of cobalt (Table 3.79 and Figure
shows that the formation of ternary complexes CoLR is 43.59% at pH 6.0. The percentage concentrations for the formation of L and HR continuously decreases with increasing pH. The percentage concentration of ternary complex ZnLR and CoLR species increases with increase in pH, confirm the formation of ternary complexes and possible equilibria in the formation of ternary complexes can be expressed by the equation 3 and 4.
4.12 References