PHYSICOCHEMICAL STUDIES OF DRUGS AND THEIR INTERACTION WITH METAL IONS

ABSTRACT

THESIS

SUBMITTED FOR THE AWARD OF THE DEGREE OF

Doctor of Philosophy

IN

CHEMISTRY

BY

SHAISTA BANO

DEPARTMENT OF CHEMISTRY
ALIGARH MUSLIM UNIVERSITY
ALIGARH (INDIA)

2010
ABSTRACT

This thesis describes the interaction of drug with metal ions and their determination by UV-visible spectrophotometry, spectrofluorimetry, resonance Rayleigh scattering (RRS), second order scattering (SOS) and frequency doubling scattering (FDS). They have been analysed in pharmaceutical formulations based on the formation of complex with metal ions. The sensitivity of these methods has also been compared with trivial analytical techniques. The stability constant and molar ratio of drug to metal has been determined.

The absorbance and fluorescence spectral pattern of levosulpiride in absence and presence of first row transition metal ions has been studied at room temperature under physiological conditions. The fluorescence spectra of the drug in presence of different concentrations of transition metal ions showed enhancement in fluorescence intensity of levosulpiride. The photophysical changes owing to the direct interaction between metal ion and the amide nitrogen of levosulpiride has been discussed in terms of CHEF (chelating enhancement fluorescence) effect. The absorption spectra of the drug at different pH exhibited two isosbestic points at 255 and 275 nm respectively, indicating the presence of different chemical species in
solution. The 2:1 (drug:metal) complex was determined spectrophotometrically and potentiometrically. The low value of stability constant suggests that complexes may dissolve and the drug can be absorbed. We have developed spectrofluorimetric method for the determination of levosulpiride in pharmaceutical formulations. The reaction condition were studied and optimized. The thermodynamic parameters obtained in this study revealed that the interaction process was spontaneous and ΔS-driven.

In chapter two the interaction of Captopril (CPL) with biologically active metal ions Mg(II), Ca(II), Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) has been investigated in acidic medium by fluorescence spectroscopy. The experimental results showed that the metal ions quench the intrinsic fluorescence of CPL by forming complex formation. It was found that static quenching was the main reason of fluorescence quenching. The quenching constant in the case of Cu(II) was highest of all quenchers, perhaps due to its high nuclear charge and small size. Quenching of CPL by metal ions follows the order Cu(II)>Ni(II)>Co(II)>Ca(II)>Zn(II)>Mn(II)>Mg(II). The quenching constant $K_{sv}$, bimolecular quenching constant $K_q$, binding constant $K$ and the binding sites “n” were determined together with their thermodynamic parameters at 27 and 37 °C. The positive entropy change indicated the gain in configurational entropy as a result of chelation. The process of interaction was
spontaneous and mainly $\Delta S$-driven.

In the third chapter, three simple and highly sensitive methods were designed for the determination of Cephalosporin antibiotics (CF$_i$) namely Cefpodoxime proxetil (CFPD), Cefdinir (CFDN) and Cefuroxime axetil (CFRX). The method is based on the enhancement in intensity of resonance Rayleigh scattering (RRS) and non-linear scattering such as second-order scattering (SOS) and frequency doubling scattering (FDS) intensities. All these antibiotics under this project react with Cd(II) in BR buffer of pH 3.4 to form 1:1 cationic chelate which further react with titan yellow to form 2:1 ion association complexes as a result of which RRS, SOS and FDS intensities were markedly enhanced. The increments of scattering intensities were directly proportional to the concentration of the drugs in a certain range. The detection limit for the three CF$_i$ were 1.73–2.38 ngml$^{-1}$ (RRS method), 5.12–5.67 ngml$^{-1}$ (SOS method), 6.25–7.26 ngml$^{-1}$ (FDS method) respectively. Among them the RRS method exhibited the highest sensitivity and the CFPD system was more sensitive than other antibiotic systems. The optimum reaction conditions, the effects of coexisting substances, the structure of ternary complexes and the reaction mechanism have been discussed. The methods were applied to the determination of CF$_i$ in pharmaceutical samples with satisfactory results.

In next chapter the interaction between prulifloxacin (PUFX) with Y(III)
and anionic surfactants (AS) like sodium dodecyl benzene sulfonate (SDBS), sodium dodecyl sulfate (SDS) and sodium lauryl sulfonate (SLS) was studied by resonance Rayleigh scattering (RRS), second-order scattering (SOS) and frequency doubling scattering (FDS) techniques combined with absorption spectra. The Y(III) reacts with PUFX in Britton-Robinson (BR) buffer of pH 6.5 to form a 1:2 cationic chelate which further reacts with AS to form 1:1 ion-association complex. As a result, the RRS, SOS and FDS intensities were enhanced greatly. The maximum RRS, SOS and FDS wavelengths of three ion-association complexes were located at 400/400 nm, 760/380 nm and 390/780 nm, respectively. The intensities of the scattering were directly proportional to the concentrations of PUFX in certain ranges. The detection limits (3σ) of PUFX for SDS, SLS and SDBS systems were 0.78 ngm⁻¹, 0.94 ngm⁻¹ and 1.1 ngm⁻¹ (RRS method), 2.7 ngm⁻¹, 3.3 ngm⁻¹ and 3.5 ngm⁻¹ (SOS method) and 4.2 ngm⁻¹, 4.3 ngm⁻¹ and 4.4 ngm⁻¹ (FDS method), respectively. Since the sensitivity of RRS method was higher than those of others the effect of coexisting substances on the reaction were investigated by this method. In addition, the composition of ion-association complex, the reaction mechanism and reasons for RRS enhancement have been discussed.

In fifth chapter a highly sensitive RRS method based on the redox reaction of Levothyroxine (LVT) was developed. LVT reacts with Fe(III) in
presence of HCl solution to produce Fe(II) which further reacted with 
\[ \text{Fe(CN)}_6^{3-} \] to form a charge neutralization \( \text{Fe}_4[\text{Fe(CN)}_6]_3 \) complex (Prussian blue) which forms an aggregate \( \{\text{Fe}_4[\text{Fe(CN)}_6]_3\}_n \) by virtue of hydrophobic and Van der Waals forces. This resulted in a significant enhancement in resonance Rayleigh scattering (RRS), second-order scattering (SOS) and frequency doubling scattering (FDS). The increase in scattering intensity (\( \Delta I \)) was found to be directly proportional to the concentrations of the LVT. The detection limits for the LVT were 2.8–8.0 \( \mu \text{gml}^{-1} \) (RRS method), 2.5–7.5 \( \mu \text{gml}^{-1} \) (SOS method) and 2.6–7.2 \( \mu \text{gml}^{-1} \) (FDS method), respectively. The RRS method exhibited the highest sensitivity of all other methods. The spectral characteristics of spectra, the optimum conditions of the reaction and the factors governing spectral changes were investigated. In addition, the reaction mechanism has also been discussed.

The final chapter of this thesis describes the complexation behavior and mechanism of fluorescence quenching of Telmisartan (TMST) by Y(III) and Nd(III) by fluorimetric method. The quenching was interpreted in terms of CHEQ (Chelation Enhanced Quenching). The experimental results showed that both Y(III) and Nd(III) quench the intrinsic fluorescence of TMST by complex formation without inducing any conformational change in TMST. It was found that static quenching was the main reason of fluorescence quenching. Linear
Stern–Volmer plots were obtained for both the complexes. pH of the solution was found to have a profound effect on quenching. The effective quenching was obtained at pH 7. The stiochiometry of TMST-metal complexes was found to be 2:1. The quenching constant $K_{sv}$ and association constant were determined together with their thermodynamic parameters at 25 and 35 °C. The negative $\Delta G$ values indicated that the complexation process was spontaneous. A decrease in logK with an increase in temperature and, the negative values of $\Delta H$ for the complexation showed that reactions are exothermic and, the metal-ligand binding is enthalpy driven.