CHAPTER - II

Scope and Object of the Present Work.

The fact that DNA is a defined macromolecular receptor allows a rational approach to drug design and permits a unique opportunity for studying site specific drug binding process. A wide variety of chemical compounds have been known to interact with DNA so as to induce certain structural alterations within the nucleic acid molecule, but apparently without the formation of new covalent bonds. Such interactions produce profound pharmalogical effects by interfering with biological processes in which nucleic acid participates.

Certain polycyclic hydrocarbons and nitrogen containing polycyclic carcinogens form complexes and are intercalated by native DNA in much the same manner as acridines and phenanthrenes. The binding of nitrogen containing polycyclic carcinogens to DNA is pH dependent, requiring the presence of the cationic form of the heterocyclic compound. Polycyclic hydrocarbons, which are neutral bind DNA to a lesser extent than nitrogen containing polycyclics. Apparently, electrostatic factors play an important, if not major role in the intercalation of heterocyclic carcinogens with DNA, even though hydrophobic force involved in intercalation probably determines the precise

structure of the complex.

Lerman who proposed from viscometric study the intercalation model to explain the binding of cationic dye with DNA showed that intercalation was absent for estradol, naphthalene or any other compound lacking three fused aromatic rings. Structural requirements, therefore, is an important factor of intercalation.

Keeping all these in view, the object of the present investigations have been chosen. Different aspects of the present work are as follows:

(i) Four phenothiazine dyes of different size have been synthesized. The aggregation of the dyes in aqueous solution have been studied spectrophotometrically. The dependence of the aggregation tendency on the shape and size of the dyes has been investigated.

(ii) The interaction of the four dyes with native and denatured DNA have been studied spectrophotometrically in the visible region. It is expected that binding of the dyes by DNA will be effected by the shape and size of the dyes. This may be helpful to understand the mode of dye binding with DNA.

(iii) The melting profile of the dye-DNA complex has been determined to find out the stability of the dye-DNA complexes.

(iv) The effect of solvent on dye-DNA complex has been investigated to see the relative stability of the complexes.

(v) The changes in viscosity of DNA on addition of the dyes and the accompanied elongation of the DNA molecule along its axis have been determined.

(vi) The data obtained in the present investigation have been examined in the light of different models suggested by different workers to explain binding of dye by DNA.

(vii) The importance of the interaction of nucleic acids with metal ions is evident from the discussion on the subject in the introductory chapter. The binding and relative affinity of different metal ions for DNA throws some light on the mode of action of metal ions in biological processes, where nucleic acids are involved. The potential uses of heavy metals in characterising nucleic acids have also been discussed.

Polarography may be used to study the binding of DNA with metal ions, which are polarographically active. A model for the determination of binding constant of complexes formed by DNA with polarographically active cations has been suggested. The validity of the model has been substantiated by data.