CHAPTER 1

INTERMOLECULAR INTERACTIONS
The significance of molecular interactions that exist between liquid mixtures, polymer solutions, polymer blends and drug-receptors are described. The basis of investigations of liquid mixtures is adopted to investigate the polymer solutions and hence the basis of polymer solution is justified to investigate the drug interactions. The approach to the present investigation on the basis of molecular interactions and the probable techniques of investigation are discussed.
1.0. INTRODUCTION

Ever since mankind was forced to come to terms with the fragility of human life, it has been consumed with conquering it. Is it any wonder then, than millions of Rupees each year are pumped into the research and development of drugs to combat death, disease of aging? The last fifty years have completely changed the way of biological and medical researchers to study and understand life, its development from conception to death, susceptibility to infectious and inherited diseases, in short, the molecular mechanisms of metabolic processes. This understanding lies in the ability to assess the information stored in the structure of molecule as a function of their physical and chemical properties. The more important reason is the ability to manipulate this information by virtue of changing the structure of macromolecules[1].

The functional manipulation of biological material could not generate much of what is done today by the pharmaceutical industry, if it were not for the preceding development in physics and chemistry during the 19th and 20th centuries including thermodynamics, statistical mechanics and the nature of chemical bond. The reductionist's approach—the study of chemistry and physics of life—created an enormous wealth of biochemical and genetic data available for the rational design of drugs and the manipulation of the genome.

1.2. MOLECULAR INTERACTIONS

The structure of a molecule determines its function. In turn, the structure of the molecule is determined by the forces between the atoms. The interactions between the atoms in a molecule are classified as strong or weak, depending on whether or not the
of the macromolecules is made of strong interactions such as the covalent bonds. Higher order structures like secondary, tertiary and quaternary structures are governed by weak forces and can, therefore, be disturbed by relatively small increase in temperature or a change of pH etc. Strong interactions are implicated mainly in the formation of the chemical structure, and to some extend in the formation of the molecular structure. Weak interactions, on the other hand, not only help to determine the three dimensional structure but also they are involved in the interactions between different molecules. Any interaction within a molecule or between molecules can be understood as a sum of the interactions between pairs of atoms\textsuperscript{[21]}. Depending on the specific details, physical interactions could either long range non-specific or short range specific physical interactions. The long range interactions are the first to control the repulsion or attraction between molecules, thereby determining whether the short range of interactions come into play\textsuperscript{[3]}.

From a quantitative point of view, physical interaction determines the physical properties of a substance\textsuperscript{[3]} (e.g. Melting and boiling temperature, surface tension, viscosity etc.). These weak forces are responsible for the secondary structure of molecules especially in biomolecules like proteins and nucleic acids and these are responsible for performing their biological functions\textsuperscript{[4]}. There exists a wide variety of physical interactions relevant to the structure and function: attractive or repulsive electrostatic interactions attractive electrodynamics interactions, hydrogen bonds and hydrophobic interactions\textsuperscript{[3]}. Ion-ion interaction exists between point charges where as ion-dipole interactions is a force of attraction between a point charge and a polar molecule. It is responsible for the solubility of ionic compounds. Hydrogen bonds and Vanderwaals interactions are classified as weak forces\textsuperscript{[5]}.
In general when two liquids are mixed together, the structure of each of the two liquids will change. The components change structurally in both aqueous and non-aqueous solutions. The phenomenon of preferential interactions between unlike molecules (solvation) or similar ones (association) is observed, depending on the degree of affinity between the components. Thus solvates and associates are elements of the structure of the solution. The structures of polymer solutions were studied from the same standpoint as the structure of liquids and liquid solution of low molecular weight substance [6].

1.4. INTERACTIONS IN POLYMER SOLUTIONS

Polymer blend are physical mixtures of two structurally different polymers which interact through weak secondary forces with no covalent bonds. The choice of suitable solvent for a given polymer plays an important role in deciding the end use. This depends on the nature of interactions between the polymer and the solvent [7]. Solvent can form secondary bonds to the polymer chains, can penetrate, replace the interchain secondary bonds, and thereby pull apart and dissolve linear and branch polymers [8]. The macromolecules may influence each other indirectly by way of mutual interaction with other molecules.

1.5. INTERACTIONS IN POLYMER BLENDS

In polymer blends, the manifestation of superior properties depends upon the interaction between the polymers on the molecular scale. This interaction results in an altogether different morphology of the blends ranging from single-phase system to two or more multiphase system. The phase separation behaviour of polymer-polymer-solvent mixture differs from that of ordinary liquid mixtures because of the large size of the component [9]. Various theories of polymer-solution and blends are the revised forms of
the binary interaction model for the observed phase behaviour of polymer/co-polymer blend. Recently, phase separation studies in polymer-polymer blends have attracted the attention of many workers and different techniques were employed to study the phase separation \cite{13, 14}.

Probably the best method of enhancing the miscibility of polyblends is to introduce specific interactions this concept has been utilized in developing a series of miscible polymer blends \cite{15}. The specific interactions capable of inducing polymer miscibility include hydrogen bond, ion-dipole, dipole-dipole, dipole-induced dipole interactions etc. \cite{16, 17}. The blends may be homogenous or heterogeneous on a macroscopic scale. Compatible and incompatible refer to the degree of intimacy of blends, which depends on the method of measurements employed in the examination.

It should be noted that in the theory of dilute polymer solution the solvent is usually treated as a continuous medium and not on the molecular level. The main aim of the study is to bring out the structural changes associated with the formation of the mixtures of polymer solute and solvent due to molecular interactions between them. The molecular interaction in the polymer blend can be examined by the sophisticated experimental and theoretical techniques. Such techniques include studies in viscosities, heat of mixing, mechanical properties, glass transition temperature and morphology by electron microscopy \cite{18, 19}. Recently, ultrasonic and FTIR have become powerful tools of investigation \cite{20}.

1.6. DRUG ACTION

The action of a drug is ascertained by its chemical structure as well as its physicochemical properties. Due to this reason, pharmaceutical chemistry is closely related to physical and colloid chemistry. At its present stage, the pharmaceutical
of analysis of drugs and calculations in pharmaceutical analysis have been based on the
general laws of these sciences [21]. The manner in which drugs act has long been of
primary concern to scientist. Since the early twentieth century, efforts have been devoted
to determine a rational explanation of drug effects in biologic systems. It is limited only
by our ability to correlate the observed physiologic event with a reasonable hypothesis
or concept [22]. Since the time of Enrich and Langley, however, the concept of receptive
substances or receptors has been used with greater and greater frequency in explaining
drug effects.

Ariens has indicated that the use of words such as receptor or active site, such
terms are useful in discussing drug action on a molecular level. In the future, as our
knowledge of receptors increases, it would be expected that the receptor concept would
be replaced by more specific terminology for the biologic component in drug action. As
an outgrowth of the receptor concept of drug action, one finds increased emphasis on the
important of physical-chemical properties of the drug and the relation of such properties
to biologic action. The physical-chemical is used here to refer to both the physical and
the chemical properties of the drug molecules that may have a bearing on the biologic
effect. A consideration of these physical-chemical properties is fundamental in
discussing several important aspects of the overall drug effect [22].

A direct interaction of the drug with receptor material (i.e., a biomacro-molecule
or biopolymer) is considered to initiate the sequence of events leading to the observed
response. In such an interaction, the chemical reactivity of the drug plays an important
role as reflected in bonding propensities and exactness of fit on the receptor. The drug
molecules with the requisite donor-acceptor groups, such as hydroxyl, carboxyl, keto,
amino and sulfhydryl groups may potentially hydrogen bond with the receptor groups [22].
receptor interactions. Bonding interactions involving nonpolar groups fall within the classification of the highly distance-specific vanderwaals interactions. Of particular interest here are the London dispersion forces (induced dipole-induced dipole), and to a much lesser degree the Debye forces (dipole-induced dipole). The strength of these interactions, the forces among atoms, can be categorized according to their thermodynamic and kinetic behaviour and is defined as affinity.

1.7. FACTORS AFFECTING ACCESSIBILITY OF DRUG TO THE ACTIVE SITE

In an intact organism, there are other important factors in the therapeutic action that follows administration of a drug. This may involve alteration of the chemical structure of the drug molecule, which may hinder or enhance the biologic effects. For most drug molecules, penetration of cell membranes is related to the lipid solubility, therefore, is an important physical property governing the rate of passage through a variety of membrane barriers.

Most drugs are either weak acids or weak bases and can exist in either the unionized or the ionized state. This property of drug molecules can greatly affect passage across biologic membranes. Unionized molecules have greater lipid solubility, and therefore the unionized molecule can penetrate most membrane barriers more readily than the ionized form of the drug. The distribution of drugs to varies tissues of the body, as well as varies membranes, depends a great deal upon the physical-chemical properties of the drug. Of greater importance is the degree of drug distribution between fat and blood. Extend and site of this accumulation can influence the potency and duration of action of a drug. The drug is therefore removed from the plasma and site of action by redistribution or accumulation in fat and muscle [22].
Many scientists believed that human diseases might be treated with preparations which would kill selectively pathogenic microbes without affecting man. Antibiotics are used as inhibitors of some reactions. For e.g., an antibiotic can inhibit specifically separate stages of protein synthesis on ribosome's (chloramphenicol, tetracycline), while other inhibit synthesis of nucleic acids at various stages. Since the discovery of antibiotic, tetracycline in 1947 by Duggar, tetracycline and several of its derivatives have been widely applied. Besides new applications, e.g., as inhibitors of metalloproteinase activity, tetracyclines have attracted much interest in the field of tetracycline-dependent gene regulation.

It has been proposed that the biological activity of the tetracycline antibiotics may involve the participation of non-ionic and zwitterionic molecular species depending upon their interconversion in the thermodynamic environments of aqueous and lipid phases. The possible biological significance of the non-ionized free base has recently been questioned. Terada and Inagi have demonstrated by ultraviolet and infrared spectroscopy that tetracycline free base, TC(0), is non-ionized in the organic solvents. The analysis clearly demonstrates that the two molecular species are in aqueous/organic solvent-dependent conformational equilibrium. Furthermore, the two molecular forms are readily interconvertible and this interconversion occurs at physiological temperatures. Methacycline, minocycline and doxycycline hyclate are of chemically modified tetracycline in which the newly synthesized derivatives have a markedly different excretion pattern from the parent compound. Doxycycline hyclate resembles both methacycline and 6-demethyl-7-chlortetracycline in chemical stability, and excreted much more slowly from the body, thus permitting use of a smaller dose.
For the present investigation the antibiotic doxycycline hyclate, a derivative of tetracycline, is taken due to its significant physiological behavior with insulin and fatty acids at physiological temperatures. A predominant hypoglycemic effect with the interactions of insulin and a noticeable antibiotic resistance with fatty acids are the two physiological phenomena which occur on the basis of specific interactions of drug actions. By molecular weight 512.94, the doxycycline hyclate is non-Newtonian molecule and exhibits zwitterionic conformations in aqueous environment and a nonionic conformation in organic solvents \[25\]. The dual character of macromolecule doxycycline hyclate is of interest for its molecular interactions with insulin in aqueous environment and interactions with fatty acids in non-aqueous environment. The low cost and simple techniques of dilute solution viscometry and ultrasonic are effective in identifying the specific interactions in dilute solutions. These techniques have been employed for thorough investigation of molecular interactions in polymer blends. The refractometric technique and FTIR are employed as conformational techniques to identify the molecular interactions in the polymer blends. Therefore as a test of validity of investigation by viscometric, ultrasonic, refractometric and spectroscopy, an investigation is attempted in the blends of Poly (methyl methacrylate) (PMMA) and Nitrocellulose (NC) in common solvent ethyl methyl ketone (EMK). On agreement and satisfaction these techniques are employed to identify the specific interactions experienced by the antibiotic doxycycline hyclate (DOX) with human insulin Actrapid (HIA) and six essential fatty acids.


