CHAPTER I

Introduction

Food additives are substances which are added to foods to preserve flavor or enhance its taste and appearance. Sometimes they are added to increase the nutrition values of the food [1]. They are added during the processing or making of the food. Food additives are playing an important role in the development of food engineering and science. We also need to know the action of the food additives for the proper understanding of food chemistry. On the other hand a drug is a chemical substance used in the treatment, cure, prevention or diagnosis of disease or used to otherwise enhance physical or mental well-being [2]. The activity of drugs in biological system is very difficult to understand and their mechanism of action is often not understood, but to understand the process different physic-chemical properties such as density, viscosity are used as tools [3-7]. Most of the biological and chemical reactions occur in aqueous phase and solvation or hydration plays a crucial role in various processes taking place in solution phase and thus studying the solvation processes is important for understanding solvent effects on chemical reactions. Therefore the introductory part of the thesis deals with a brief discussion on the food additives and drugs, general application of food additives and drugs and the solvation phenomenon including various interactions occurring in solution phase viz. solute-solute or ion-ion interactions and solute-solvent or ion-solvent interactions.

1.1. Food additives and drugs

Food is one of the main basic requirements for human being. Basically we get food both from plant and animal sources (exceptions: few fungi, algae etc.) [8]. Generally foods are being processed before their consumption. The processing may vary depending upon the nature of the food. In some cases essential nutritive additives are added to the food. Food additives are added in the foods before the heat treatment to give the food its required flavor, taste and texture [1]. To attain a balance diet salts, vitamins and amino acids are also added in the foods [9]. Some time foods are processed for its future use and to prevent its rancidity some additives (salting) are added. Food additives are added to the food to perform some specific role, such as preservation of food stuffs by increasing its shelf life, preventing the growth of microbes. Other role includes addition of some special flavor and color in the food stuffs. Food additives may be naturally occurring or artificially prepared. Artificial additives are replicas of naturally occurring additives, prepared depending upon the requirement. There are a number of food additives commonly used including vitamins, amino acids, acids, antioxidants, acid regulators, coloring agents, sweetener, emulsifier, thickeners, food supplements and preservatives. Food antioxidants play an important role in the food industry. Oxidation process brings destructive reaction in food stuffs by producing free radicals. Antioxidants neutralize the production of free radicals by donating their own electrons to the free radicals [10]. Antioxidant delays the lipid oxidation process in foods. Antioxidants are also used as therapeutic agents for medicinal uses. Basic criteria for a substance used as an antioxidant in food to be effective at low concentration, should not posses any unwanted aroma and color, should be heat sensitive, non volatile and must carry the characteristics in the food. Plants contain a number of naturally occurring antioxidants e.g., ascorbic acid, beta-carotene, gallic acid, xanthophylls, bioflavonoid and tannins. Nutritive additives vitamins, amino acids and minerals are also important in food processing industries. Vitamins are needed in small quantities to sustain life. They promote the immune system and boost the development and growth [11]. Generally vitamins are found in foods but sometimes they are added to food to increase its nutritive values. Amino acids are used as the building block of the proteins and also act as the intermediate in the metabolism process [12]. Minerals are essential for body to stay healthy [13]. The body uses different minerals to perform specific functions from transmitting nerve impulses to make strong bones. Minerals also needed to make hormones. Acid regulators maintain the required acidity or basicity of food stuff, which is important for food processing [14]. Few examples are acetic acid, lactic acid, malic acid, calcium acetate. To make food attractive different eatable dyes are added to foods as coloring agents. It can be a dye, a pigment or any substance that can impart colors alone or through reaction with other substances. Some examples are ferrous gluconate, saffron, lucine, carmine etc [15]. An emulsifier is a substance which has both hydrophilic and hydrophobic parts in it. It is generally used to make homogenous and smooth emulsions [16]. Egg yolk has been used in the preparation of mayonnaise as an emulsifier. In chocolate, emulsifiers are used to reduce viscosity and permitting a reduction in the amount of cocoa butter, which reduces both cost and calories. Emulsifiers are used in cakes for its better release from pans. Sweeteners used in food stuffs to impart sweet taste. Non nutritive sweeteners provide generally less energy to the food so useful for certain health conditions like diabetes, obesity while nutritive sweeteners provide energy with sweet taste in the food [17]. Few examples of non nutritive sweeteners are saccharin, aspartame, acesulfame potassium, sucralose, neotame, stevia etc. nutritive sweeteners are generally saccharides like fructose. All the food additives used in food stuffs must be approved by FDA. The action of food additives is very difficult to understand. But we can get some information about the different interactions performed by food additives by volumetric and rheological properties [18-37].

On the other hand in medicinal chemistry the chemist attempts to design a medicine or pharmaceutical agent which will benefit mankind, such a compound can be called as drug [38]. Generally a drug is any substance other than food, that when inhaled, injected, smoked, consumed, absorbed via a patch on the skin or dissolved under the tongue causes a physiological change in the body. Drugs can be classified based on the pharmacological action e.g., analgesics, antipsychotics, antihypertensive, antiasthmatics, antibiotics, etc., by chemical structure e.g., penicillins, barbiturates, opiates, steroids, catecholamines, etc., by target system e.g., antihistamines, cholinergics, etc and by site of action. The blood stream carries the drug in the body. Liver contains certain enzymes modify the drugs. This is called drug metabolism. The metabolized drug then recirculated in the body through the blood stream where they work as medicine [39]. When the drug moves throughout the body by blood streams it interacts with vitamins, minerals, amino acids, hormones, carbohydrates etc. present in the body. Most of the drugs are insoluble in water, they are administrated as hydrochlorides or other salt form. So they are amphipathic in nature due to presence of both hydrophobic and hydrophilic groups in the same molecular moiety. So their solvation is very much interesting as far as their structure and interactions in biological fluids. Physico chemical measurements may be used as a tool for observing such interactions [40-61].

1.2. Application of food additives and drugs

A large number of food additives are used in modern day food processing industries depending upon the need. Drugs are used by human being from ancient times in different forms. Today medicinal chemistry is a subject of interest due its major applicability in mankind. Thus some important applications of food additives and are outlined here.

1.2.1. Uses of food additives

Food additive performs the following functions in food stuffs.

I. Food preservatives delay the spoilage of food and thus increase the shelf life of food, it also preserve the appearance of the food. Vinegar, benzoic acid, parahydroxy benzoic acid ester [62], sodium nitrate, sulfur di oxide are used as food preservatives. Vinegar is used for pickling. Sulfur di oxide is used in wine industry. Soft drinks, fruit juices are preserved with benzoic acid.

II. Antioxidants are also a type of food preservatives used as free radical scavangers. Ascorbic acid, Gallic acid [63-64], butylated hydroxyanisole are examples of antioxidants. Antioxidants commonly added to cheese, chips, oil as they suppressed the formation of hydro peroxide. Ascorbic acid and ascorbates are mainly used in cheese and chips preparation, it is also used as flour improver. Gallic acid and propyl gallets are used in foods that contain oil and fat.

III. Coloring agents are added to the food stuffs to enhancing naturally occurring colors, protects flavor and vitamins from damage by light, increase the appetite appeal, to mask defects and to keep the food tasting fresher for longer time [1]. Antocyanin used in soft drink and pickles. Annatto used in diary and fat products. Saffron used in baked goods. Lucin used in ice cream, sugar and flour.

IV. Sweeteners are used to give sweet taste to the food. It is called the sugar substitute [65]. High-intensity sweeteners are ingredients used to sweeten and enhance the flavor of foods. Because high-intensity sweeteners are many times sweeter than sugar i.e., sucrose, smaller amounts of this sweetener achieve the same level of sweetness as sugar in food. People may use high-intensity sweeteners in place of sugar as they only contribute a few calories to the diet. High-intensity sweeteners also generally will not raise blood sugar levels. Saccharine, aspartame, sucralose, advantame are used as sweeteners in baked goods, soft drinks, powdered drink mixes, candy, puddings, canned foods, jams and jellies, dairy products, and scores of other foods and beverages.

V. Thickeners, stabilizers and emulsifiers are also used as food additives. They are used to bring homogeneity in the food stuff. Alginic acid is a natural polysaccharide and used in dairies, sauces and bakeries. Sorbitol and mannitol is a natural carbohydrate alcohol used as humectants in baked goods. Sodium or calcium stearoyl-2-lactylate used as emulsifier in bakery.

VI. Nutritive additives like vitamins and amino acids are added to food to increase its nutritional values. Thiamine hydrochloride, riboflavin (Vitamin B_2), niacin, niacinamide, folate or folic acid, beta carotene, potassium iodide, iron or ferrous sulfate, alpha tocopherols, ascorbic acid, Vitamin D, amino acids (L-tryptophan, L-lysine, L-leucine, L-methionine) are examples of the food additives. They are used in lour, breads, cereals, rice, macaroni, margarine, salt, milk, fruit beverages, energy bars, instant breakfast drinks.

VII. pH Control Agents are generally used to control the acidity or basicity of a food to prevent its spoilage. Examples of this kind of additives are Lactic acid, citric acid, ammonium hydroxide, sodium carbonate. They are used in Beverages, frozen desserts, chocolate, low acid canned foods, baking powder.

VIII. Firming Agents are used to maintain the crispness and firmness of the food. Calcium chloride, calcium lactate is used as firming agents and used in processed fruits and vegetables.

IX. Flavor Enhancers enhance flavors already present in foods. Monosodium glutamates (MSG), hydrolyzed soy protein, autolyzed yeast extract, disodium guanylate are used as flavor enhancer in many processed food.

X. Humectants are used to retain moisture. Glycerin, sorbitol are used as humectants in Shredded coconut, marshmallows, soft candies, confections.

1.2.2. Uses of drugs

Drugs are used to cure or prevent diseases. There are many types of drugs depending upon their action. Few examples are appended below.

I. Antipyretics are used to reduce fever [66]. Ibuprofen and aspirin are examples of this kind of drug.

II. Analgesics are used to reduce pain. Paracetamol, morphine is used analgesic drugs [67].

III. Chloroquine, amodiaquine, sulfonamides are used as antimalarial drug. They are used for the treatment of malaria.

IV. Antibiotics like tetracycline, sulfacetamide, erythromycin are used for the bacterial infections.

V. Boric acid, cetyl trimethylammonium bromide, bezalkonium chlorides are examples of antiseptic drugs. They prevent sepsis.

VI. Amphetamine, dextroamphetamine, epinephrine are used as stimulants. Generally they are physic active drugs that improve the mental condition.

VII. Metformin, glimepiride, pioglitazone, acarbose are few examples of antidiabatic drugs. They control the sugar level in body.

VIII. Ketamine, propofol, etomidate are used as anesthetic drugs.

IX. Zidovudine, Retrovir are used as anti HIV drugs.

X. Bleomycin, Epirubicin, Etoposide, Paclitaxel, Irinotecan, Carboplatin, Cisplatin are some anti cancer drugs.

XI. Lovastatin, fluvastatin are used as lipid lowering drugs.

XII. Sodium valporate, lamotrigine, carbapamazepine are used as anticonvulsant drugs or mood stabilizers.

1.3. Water activity in Food

Water or moisture is one of the vital constituent in many foods. In a hydrolytic process, it acts like a reactant and as a medium water supports many chemical reactions. Removal of water from food may inhibit the growth of microorganism, thus improving the shelf lives of many foods. Through the physical interaction with vitamins, proteins, polysaccharides, salts, water contributes significantly to the texture of the food. The function of water is better understood when its structure and state in the food system are clarified. In modern food technology, food stuff has dried or frozen to ensure a wholesome quality for a long period of time. It is therefore necessary to know the effect of water on storage life. Scott concluded that the storage quality of a food is directly depending upon the water activity. Decrease water activity retards the growth of microorganisms and thus slows down the enzyme catalyzed reactions. One of the options for decreasing water activity is to add food additives with high water binding capacity. Glycerol, sorbitol and common salts may be used to serve this purpose. The physical state of metastable foods depends on their composition, on the temperature and on the storage time. Depending on temperature the phase could be glassy, rubbery or highly viscous. Foods become plastic when their hydrophilic components are hydrated. Thus water content affects the temperature. The rate of food's chemical and enzymatic reactions as well as that of physical processes becomes almost zero when the food is stored at the phase transition temperature. Thus measures to increase storage life by increasing phase transition temperature can include the extraction of water through drying or an immobilization of water by means of freezing, or by adding polysaccharides.

1.4. Solvent Effects

Most of the chemical and biological processes occur in solution phase. The role of solvation in chemistry and biology is obvious. The influence of the solvent on chemical phenomena has been observed for a long time and it has received the attention of researchers from both experimental and theoretical fields related to chemistry. The presence of a solvent influences the outcome of a chemical reaction through the interaction of the local environment with the individual species undergoing the reactions. The solvent, on one level, provides an energy path for the stabilization of energetic products formed during reactions and provides physical barriers to the motion of the reactive species. On a more subtle level, the solvent perturbs the potential energy curves that govern these reactions [68]. Since the solvent species around a solute form a structure that determines the outcome of chemical and/or biological events, the solvent species are not just "spectator" species but are part of the chemical or biochemical process. Solvation has been proved to be of fundamental importance in diverse areas like biological activities and atmospheric processes [69]. Solvated ions appear in high concentrations in living organisms where their presence or absence can fundamentally alter the functions of life. Ions solvated in organic solvents or mixtures of water and organic solvents are also very common [70] and the exchange of solvent molecules around ions in solutions is fundamental in understanding of the reactivity of ions in solution [71]. Solvated ions also play a key role in electrochemical applications simply because the conductivity of electrolytes depends on the ion-solvent interactions [72]. Majority of the chemical reactions are usually performed in solutions and solvents can influence reactions in a number of ways. Solvents may be used as a reaction medium to bring reactants together, as a reactant to react with a solute to make it dissolved and as a carrier to deliver chemical compounds in solutions to their point of use in the required amounts.

Solvents also control the temperature in exothermic and endothermic reactions. In endothermic reactions, heat could be supplied through a heated inert solvent having a high heat capacity while in exothermic reactions, the surplus heat can be removed by allowing the solvent to boil or absorb heat. If reactions involve solid reactants, solvents could be used to create a homogenous reaction phase (i.e., solution) through which the solid reactants can be brought into contact. It is important to select the most appropriate solvent so as to get most effective results or optimum yield of the products. A good solvent should be able to meet all the necessary standards such as it should be an inert to all the reaction conditions, the boiling point of the solvent should be appropriate, at the end of the reaction there should not be any difficulty in its removal and it should dissolve the reagents and reactants. In essence, the reaction rates are influenced by differential solvation of the starting material and the transition state by the solvent. When the reactant molecules proceed to the transition state, the solvent molecules orient themselves to stabilize the transition state. If the transition state is stabilized to a greater extent than the starting material then the reaction proceeds faster. If the starting material is stabilized to a greater extent than the transition state then the reaction proceeds slower. However, such differential solvation requires rapid relaxation (re-orientation) of the solvent (from the transition state orientation back to the ground-state orientation). Thus, equilibrium-solvent effects are observed in reactions that tend to have sharp barriers and weakly dipolar, rapidly relaxing solvents.

1.4.1. Solvation

The term solvation refers to the surrounding of each dissolved molecule or ion by a shell of more or less tightly bound solvent molecules. This solvent shell is the result of intermolecular forces between solute and solvent. During the solvation process, a relatively small amount of solute dissolves in relatively large amount of solvent to form a homogeneous phase through a variety of intermolecular forces such as solvent-solvent, solute-solvent and solute-solute interactions. The solute-solute interactions gradually disappear and replaced by solute-solvent interactions during the dissolving process. The solute molecules will perturb the structure of the solvent when they enter into the solution and they create some more or less ordered solvation shell around themselves. For the dissolving process to be spontaneous, the lowering of the free energy resulting from the solvation must exceed the free energy increase due to the annihilation of the interactions that existed between the solute molecules and between the solvent molecules. If the liberated solvation energy is lower than the lattice energy, then the overall process of dissolution is endothermic and if the solvation energy is higher than the lattice energy, then the overall process is called exothermic.

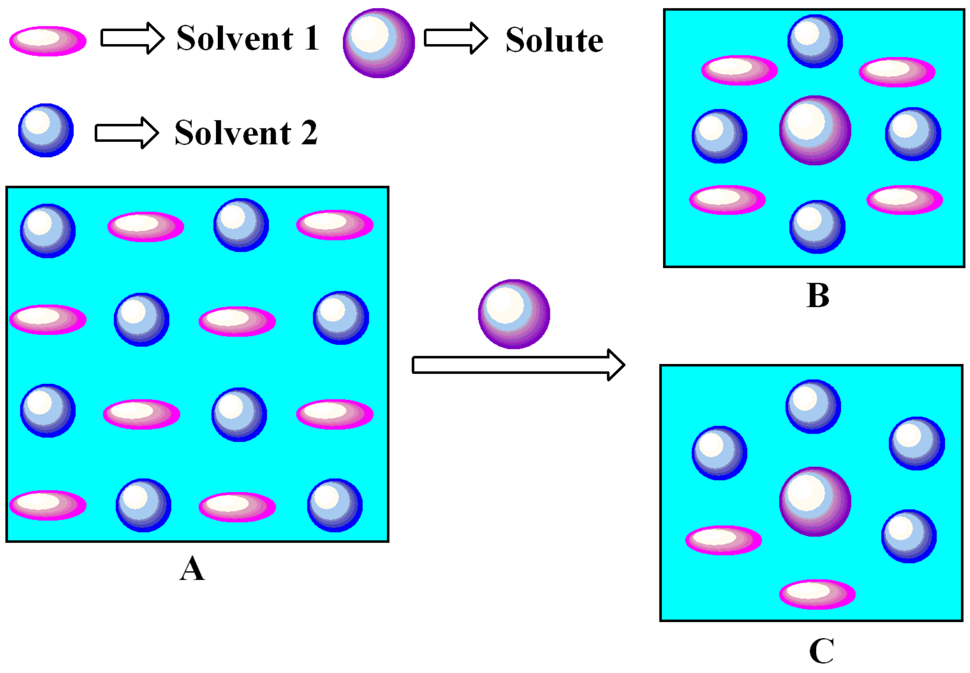

Fig. 1.1. Schematic representation of preferential solvation, A: binary mixture of solvent 1 and solvent 2; B: ideal solvation of the solute; C: preferential solvation of the solute by solvent 1.

1.4.2. Preferential Solvation

The solvation phenomena in mixture of solvents e.g., binary, ternary, etc., is more complicated than in pure solvents. In addition to the different types of interactions between solute and solvent, the interactions between solvent mixtures play a significant role in the solvation process. This leads to the large deviation from the ideal behavior expected from the Raoult's law of vapor pressure depression for binary mixture. Solute may induce a significant change in the composition of the solvent mixture in the solvation sphere than the bulk composition. This is generally known as selective solvation or preferential solvation [73]. This phenomenon is graphically represented in figure 1.1.

Preferential solvation commonly results from specific (e.g., hydrogen-bonding) and nonspecific (dielectric enrichment) [74] solute-solvent interactions. It can also be a result of solvent-solvent interactions [75].

1.5. Ion-Solvent or Solute-Solvent Interaction

The process of solvation of a solute by solvent molecules is of primary importance in many branches of chemistry such as chemical syntheses or complex formation processes. Thus solvation of ions or solutes and its source in terms of solute-solvent or ion-solvent and solvent-solvent interactions constitute an important area in chemistry, since solute-solvent or ion-solvent interactions play a major role in controlling the chemical reaction rate, chemical equilibrium position, etc. Solvent affects both molecular structure and electronic structure of solutes. Knowledge of their interactions helps in better understanding of the profile of solutes or solvents, i.e., whether the added solute modifies or distorts the structure of the solvent [76]. For a particular chemical reaction it was shown that the reactivity is influenced by the preferential solvation of the reactant and/or transition state through non-specific and specific solute-solvent or ion solvent interactions. In the solvation process, changes in energy of transition states are of critical importance. In order to analyze solute-solvent or ion-solvent interactions, great interest has been paid to the behavior of solutions of electrolytes and non-electrolytes in pure solvents and binary solvent mixtures [77-78].

Ion-solvent or solute-solvent interactions can be defined by starting with a solid ionic crystal or a neutral solid and then reducing the forces holding the ions together in the crystal or solvation of neutral molecules by some kind interactions between the solute molecules and the solvent. A stage is reached when the inter-ionic forces in case of ionic crystal are so weakened that the ions acquire a new degree of freedom that produces the mobile ions due to freedom of transnational motion. All these alterations are possible with the addition of a solvent that can influence the inter-ionic forces within the crystal and there is a considerable energy of interaction between the ions and the solvent molecules. These interactions are collectively termed as ion-solvent interactions. A schematic representation of dissolution of an ionic crystal by the action of a solvent is shown in figure 1.2.

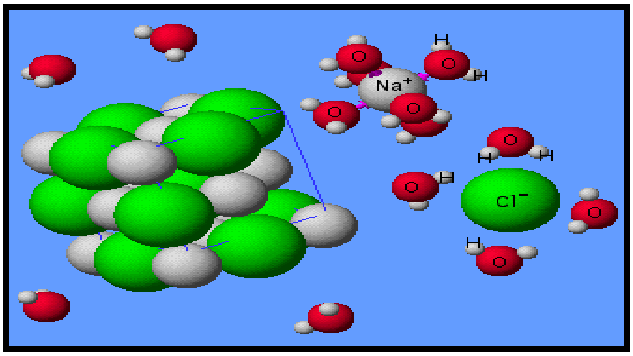

Fig. 1.2. Dissolution of an ionic crystal in a solvent.

Ions orient dipoles. The spherically symmetrical electric field of the ion may tear solvent dipoles out of the solvent lattice and orient them with appropriate charged end towards the central ion. Thus, viewing the ion as a point charge and the solvent molecules as electric dipoles, ion-dipole forces become the principal source of ion-solvent interactions. The majority of reactions occurring in solutions are chemical or biological in nature. It was presumed earlier that the solvent only provides an inert medium for chemical reactions. The significance of ion-solvent interactions was realized after extensive studies in aqueous, non-aqueous and mixed solvents were undertaken [79-80].

The organic solvents have been classified based on the dielectric constants, organic group types, acid base properties or association through hydrogen bonding [80], donor-acceptor properties [81], hard and soft acid-base principles [82], etc. As a result, the different solvents show a wide divergence of properties ultimately influencing their thermodynamic, transport and acoustic properties in presence of electrolytes and non-electrolytes in these solvents. The determination of thermodynamic, transport and acoustic properties of different electrolytes or non-electrolytes in various solvents would thus provide important information in this direction. Henceforth, in the development of theories of electrolytic solutions, much attention has been devoted to the controlling forces- ‘ion-solvent interactions’ in infinitely dilute solutions wherein ion-ion interactions are almost absent. By separating these functions into ionic contributions, it is also possible to determine the contributions due to cations and anions in the solute (ion)-solvent interactions. Thus ion-solvent interactions play a key role in understanding the physico-chemical properties of solutions.

1.6. Ion-Ion or Solute-Solute Interaction

Ion-solvent interactions are only a part of the story of an ion related to its environment. The surrounding of an ion sees not only solvent molecules but also other ions. The mutual interactions between these ions constitute the essential part- ‘ion-ion interactions’. The degree of ion-ion interactions affects the properties of solution and depends on the nature of electrolyte under investigation. Ion-ion interactions, in general, are stronger than ion-solvent interactions. Ion-ion interaction in dilute electrolytic solutions is now theoretically well understood, but ion-solvent interactions or ion-solvation still remains a complex process. As proton transfer reactions are particularly sensitive to the nature of the solvent and it has become clear that the solvents significantly influence a majority of the solutes. Conversely, the nature of the strongly structured solvents, such as water, is substantially modified by the presence of solutes.

1.7. Object and Application of the Research work

In recent years there has been an increasing interest in the study of physico-chemical properties of solute-solvent systems. The physico-chemical properties play a pivotal role in interpreting the intermolecular interactions among mixed components and efforts in recent years have been directed at an understanding of such properties at microscopic and macroscopic levels. In order to gain insight into the mechanism of such interactions thermodynamic, transport and acoustic studies on mixed solvent systems are highly useful. Most chemical and biological reactions prevail in solution phase and the understanding of chemical reactions is largely based on the behavior of reactants in the studied solutions. Solvent parameters such as dielectric constant, density, viscosity and refractive index are useful parameters in elucidating various solvent properties for explaining solvent effects in many chemical processes. Due to complexity of intermolecular interactions, the development of a generally valid model for solution is not an easy task. Thus, models with non-specific solute-solvent interactions like van der Waals interactions are mainly dealt with [83]. Many biological processes including transporting, signaling, metabolism, etc., are also controlled by solvation [84-85]. Several theoretical treatments have been developed to link quantitatively the solvent effects to the bulk properties of solvent. The simplest model amongst these treatments is given by Onsager [86] and Kirkwood [87].Various approaches were suggested over the years for ascertaining the number of solvent molecules closely associated with ions and the number of those solvent molecules released from the solvation shell of ions to the bulk on ion pair formation. Certain ions, such as transition metal cations, have geometrically well-defined first solvation shells [88] but they are further solvated in a second concentric solvation shell with much less well-defined geometries and solvation numbers. However most ions are solvated in a not clearly defined manner, not only in the closest vicinity of the ions but also beyond that, due to non-directional electrostatic ion-dipole or ion-induced dipole interactions [89]. In solution chemistry the way for proper understanding of the different phenomena regarding the molecular interactions forms the basis of explaining quantitatively the influence of the solvent and the extent of interactions of ions in solvents. Estimates of ion-solvent interactions can be had thermodynamically and also from the determination of partial molar volumes, viscosity *B*-coefficient and limiting ionic conductivities, etc.

The solute-solute and solute-solvent interactions have been subject of wide interest in many area of chemistry. The influence of these solute-solvent interactions is sufficiently large to cause dramatic changes in chemical reactions involving ions. The changes in ionic solvation have important applications in diverse areas such as organic and inorganic synthesis, studies of reaction mechanisms, non-aqueous battery technology and extraction [90]. Knowledge of ion-solvent or solute-solvent interactions in aqueous solutions is very important in many practical problems concerning energy transport, heat transport, mass transport, reaction kinetics and fluid flow. Besides finding applications in engineering branch, the study is important from practical and theoretical point of view in understanding liquid theories. The aqueous systems have been of immense importance to the technologist and theoretician as many chemical processes occur in these systems.

In recent years, there has been increasing interest in the behavior of food additives and drugs in different aqueous solvents with a view to investigate solute-solute and solute-solvent interactions under varied conditions. A proper understanding of solution properties may help in elucidating their behavior in solution phase.

Literature survey reveals that a number works on the thermodynamic properties of food additives and drugs in aqueous solvent or mixed aqueous solvents have studied [18-37, 40-61, 91-97].

Studies on thermodynamic properties of these food additives in solution phase may provide valuable information regarding their solution behavior, taste effect and shelf life of different food components [18-37]. Thermodynamic properties of drugs in different aqueous media give us appropriate understanding of the drug effect, also the solvation of drugs [40-61]. Their physico-chemical properties would enable chemists to choose different aqueous media that will enhance the effect of drugs and solubility. Thus studies on transport properties of food additives and drugs along with the thermodynamic properties would give valuable information about different molecular interactions in their solutions. The influence of these solute-solvent interactions is sufficiently large to cause dramatic changes. Also it is apparent that the real understanding of the molecular interactions in solution phase is a difficult task. The aspect embraces a wide range of topics but we have embarked on a series of investigations based on the volumetric, viscometric, refractometric, and spectrophotometric methods to study the chemical nature of the structure of solutes and solvents and their mutual and specific interactions in solution.

1.8. Importance and Scope of the Physico-Chemical Parameters

The solvation of solute is of primary importance in many fields ranging from synthetic chemistry to biological phenomenon. It is well known that the solvation process is complex since the solvation process is affected by the behavior of both solute and solvent resulting from their molecular structure as well as hydrophilic-hydrophobic properties [98]. Fundamental thermodynamic and thermophysical properties are essential sources of information necessary for a better understanding of the non-ideal behavior of complex systems, because of the fact that physical and chemical effects are caused by molecular interactions, intermolecular forces, etc. of unlike molecules [99]. The studies of physico-chemical properties involve the interpretation of the nature of intermolecular interactions among the mixed components. The interactions between molecules can be established from a study of some physical parameters such as density, viscosity, conductance, refractive index as well as electronic spectroscopy and infrared spectroscopy, etc [100-101]. From a practical point of view, these properties are necessary for the development of thermodynamic models required in adequate and optimized processes of the chemical, petrochemical, pharmaceutical and food industries. Measurement of thermodynamic and transport properties such as density and viscosity of solutes in pure solvent and binary solvent mixtures at various temperatures are useful to understand the nature of interactions occurring in solution and helpful to practical chemical engineering purposes [102].

Density of solution and related volumetric properties are essential for theoretical as well as practical aspects. The density is useful in conversion of concentration unit and in the investigation of interactions in solutions. The density of fluid is an important parameter for research and industrial fields. Density is used to solve a variety of problems such as quality control in the production of industrial liquids or concentration determination in the food and beverage industries as in measuring sugar and alcohol concentration. The density data are used to calculate the apparent molar volumes and partial molar volumes at infinite dilution. Apparent molar volumes and partial molar volumes give a direct measure for displacement of solvent by solute and thus reflect the compatibility of the solute with the solvent. Studies of the apparent molar volumes and partial molar volumes of electrolytes and non-electrolytes are used to examine the ion-ion/solute-solute, ion-solvent/solute-solvent and solvent-solvent interactions. In addition, density is required for the estimation of other chemical properties such as molar refraction and viscosity, etc.

Knowledge of viscosity of fluids is essential in most engineering calculations where fluid flow, mass transport and heat transport are important factors. Viscosity is the property of a fluid liquid or gas that mainly characterizes its flow behavior. Viscosity varies with temperature and in general, the viscosity of a simple liquid decreases with increasing temperature and vice-versa. Viscosity data provides valuable information about the nature and strength of forces operating within and between the unlike molecules. Recently the employment of computer simulation of molecular dynamics has lead to significant improvement towards a successful molecular theory of transport properties in fluids and a proper understanding of molecular motions and interaction patterns in non-electrolytic solvent mixtures involving both hydrogen bonding and non-hydrogen bonding solvents [103-104].

Viscosity measurement has also proved to be a valuable tool for the physical chemist, since the viscosity coefficient is profoundly influenced by the size, shape and arrangement of the molecules. Also a potentially rewarding approach in the study of ion-solvent interaction involves the estimation of the free energy and related thermodynamic quantities for the transfer of individual ion or solute from one solvent to another [105].

Acoustic properties are powerful tools to analyze the behavior of various solutes such as vitamins, amino acids, carbohydrates, ionic liquids, drugs in aqueous and non aqueous solutions. The study of propagation of ultrasonic waves in liquid systems is particularly well adapted to examining changes in physical properties at the macro level [106-107]. Ultrasonic velocity and their variation with temperature and concentration help to understand the nature of molecular interactions in mixtures. As speed of sound is highly sensitive to the structure and interactions present in the solution therefore for quantitative estimation of the molecular interactions in the solution ultrasonic velocity approach may be employed [108].

The study of physico-chemical behavior of solute in solution from refractive index measurement has gained much importance. In electrolytic solution ion-ion, ion-solvent and solvent-solvent interactions can be fully understood from the refractive index studies [109]. Refractive index is one of the important properties of a liquid or solution and refractive index can be measured easily with a high degree of accuracy. The molar refractivity reflects arrangements of the electron shell of ions in molecules and yields information about the electronic polarization of ions. The molar refractivity measures the change in the properties due to polarization or deformation of the electron shells of ions under the influence of neighboring surroundings [110].

Again in a solute-solvent system the electronic interactions of various electronically excited states of the solute and solvent molecules may be also substantial. When absorption spectra are measured in solvents of different polarity, it is found that these solvents modify positions, intensities and shapes of the absorption bands. These changes are results of intermolecular solute-solvent interaction forces such as ion-dipole, dipole-dipole, dipole induced dipole, hydrogen bonding, etc. The interaction force tends to alter the energy difference between ground and excited state of the absorbing species containing the chromospheres. Thus, solvent effects on absorption spectra can be used to provide information about solute-solvent as well as solvent-solvent interactions. These facts, therefore, prompted us to undertake the study of solution behavior of some food additives and drugs in different solvent media: a physico-chemical study. Furthermore, the thermodynamic properties derived from experimental density, viscosity, sound velocity and refractive index data and subsequent interpretation of the nature and the strength of intermolecular interactions helps in testing and development of various theories of solution.

1.9. Importance of Solutes and Solvents Used

The importance of solutes and solvents used in the works embodied in this thesis is outlined below.

1.9.1 Solutes and cosolutes

Ascorbic acid (vitamin C) is a naturally occurring water-soluble vitamin with antioxidant properties. It is not only required for the metabolism of folic acid, tyrosine, phenylalanine, histamine, *etc.*, but also essential for the synthesis of collagen that contributes to the structure of muscles and bones [111]. It is used an anti-ageing agent as it protects the body tissues and cells against oxidative damage from free radicals and reactive oxygen derivatives. It improves the elasticity of skin and thus reduces wrinkles due to its involvement in proline and lysine hydroxylation in collagen biosynthesis. Deficiency of ascorbic acid in human can cause several diseases like scurvy, anemia, gum problems, muscle degradation and neurotic disorders, *etc*. It is mainly applied to food and feed to increase product stability and quality. So ascorbic acid is added to foodstuffs to retain its characteristic aroma, nutrients and other properties during processing or before packing [112].

Thiamine or vitamin B_1 is a water-soluble vitamin. Being a coenzyme or their precursor for several major enzyme complexes (such as α–ketoglutarate dehydrogenase, pyruvate dehydrogenase and transketolase, *etc.*), it is crucial for carbohydrate metabolism and genetic regulatory processes [113, 114]. It is also necessary for normal development and function of the brain and nerves [115]. Thus vitamins such as vitamin B_1 are essential nutrients for human body. But vitamins are not synthesized within the body and thus are must be supplemented in the food staffs as a food additive [116]. Phosphate derivatives of thiamine are involved in many cellular processes. It is required for the biosynthesis of neurotransmitter acetylcholine and γ-amino butyric acid. It is also used for digestive problem including poor appetite and ulcerative colitis. People also take thiamine for conditions related to low levels of thiamine including beriberi and inflammation of the nerves. Hence it finds widespread application as an additive in food and drug.

Nicotinic acid has gained huge attention because of its versatility in terms of chemical, biochemical and therapeutic applications [117]. This derivative of pyridine has a molecular formula $C_6H_5NO_2$ with a carboxyl group (-COOH) at the 3-position and it is sometimes called niacin or vitamin B_3 in combination with nicotinamide [117-119]. It is a colorless water-soluble compound and it could be converted to NAD and NADP *in vivo* in pharmacological doses. It reverses atherosclerosis by reducing total cholesterol, triglycerides and lipoproteins. It also plays a crucial role in both DNA repairing and the production of steroid hormones in the adrenal gland. Hence it finds widespread uses as an additive in food, forage and cosmetics [120-121].

Pyridoxine hydrochloride, or vitamin B6, is a water soluble vitamin which is important for more than 100 enzyme reactions in body [122-123]. Pyridoxine HCL is mostly related to the metabolism of amino acids and proteins [124]. It helps the body convert food into fuel; maintain proper functioning of nerves, and produce red blood cells. Vitamin B6 is found in many foods. It is added to foods, and is available as a dietary supplement. Its deficiency directly related to immune system of body [125].

Amino acids are the basic units of protein molecules and they are used as protein model compounds [126-127]. Normally proteins are digested in body and amino acids left, and these amino acids are further used to produce proteins. Amino acids are used in a number of metabolism processes in body. They are also used as food additives. Food additive codes of glycine and alanine are E640 and E639 respectively, as per U. S food and drug administration.

Lactose is a milk sugar composed of one galactose and one glucose molecule. It has significant role in the biological and food industrial processes [128]. Food producers use lactose as filler in bread. As lactose does not have any flavor so using lactose in food does not change its flavor. In food industries it is used as an alternative sweetener. Additionally, as lactose can help to prevent food discoloration it can be used in canned and frozen vegetables. Most of the powdered food products such as soups, meal-replacement supplements and dehydrated potatoes generally contain lactose. Further some non-dairy foods like coffee creamers contain lactose in the state of dry milk solids or whey. In the pharmaceutical industry, lactose is used as a coating or filler in many prescription and over-the-counter drugs including birth control pills, antacids, vitamin pills and throat lozenges because of its excellent compressibility properties [129-130].

Paracetamol also known as acetaminophen or N-acetyl-p-amino phenol is a mild analgesic, antipyretic agent and also a non-steroidal anti-inflammatory drug [131-133].

Betaine hydrochloride drug (B.HCl) is used for supplementing low stomach acid which is a key component of our immune system and it is also as a digestive pill for the human body. In some cases it may also used for the treatment of food allergies, diarrhea, thyroid disorder and low level of potassium [77].

Metformin hydrochloride (M.HCl) is used as an antidiabatic and antihyperglycemic agent to control both basal and postprandial elevated blood glucose in patients with non-insulin dependent type II diabetes mellitus [134]. Metformin hydrochloride decreases glucose production and also its absorption in intestine. It is also used in the treatment of polycystic ovary syndrome.

All the drugs and food additives used as solute are shown in fig. 1.3 and 1.4.

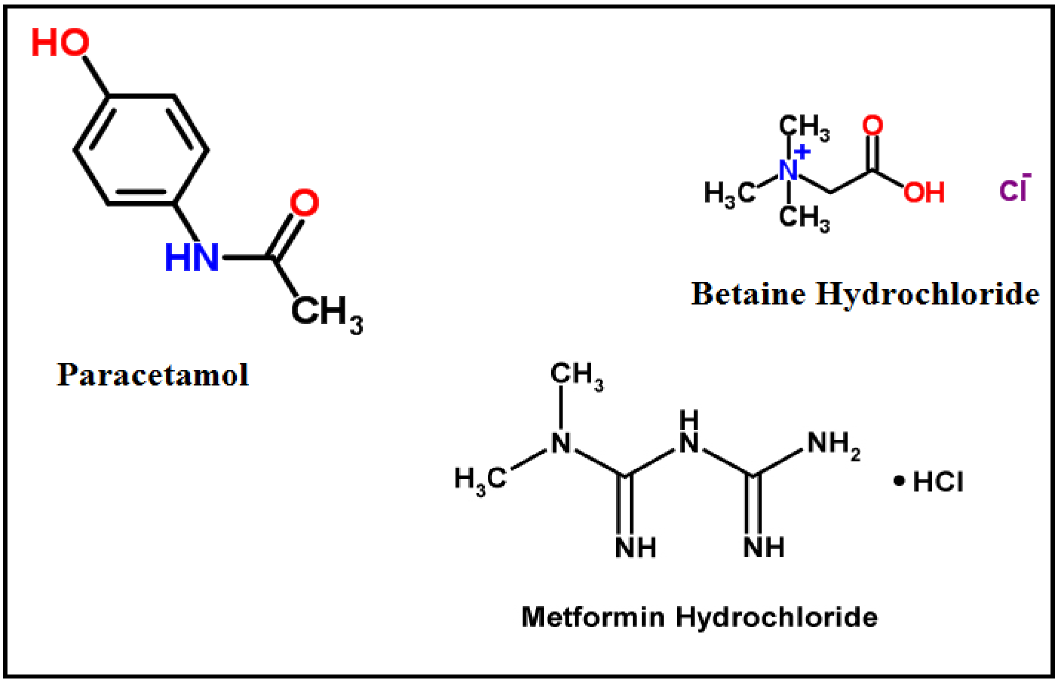

Fig. 1.3. Structures of used drugs as solutes.

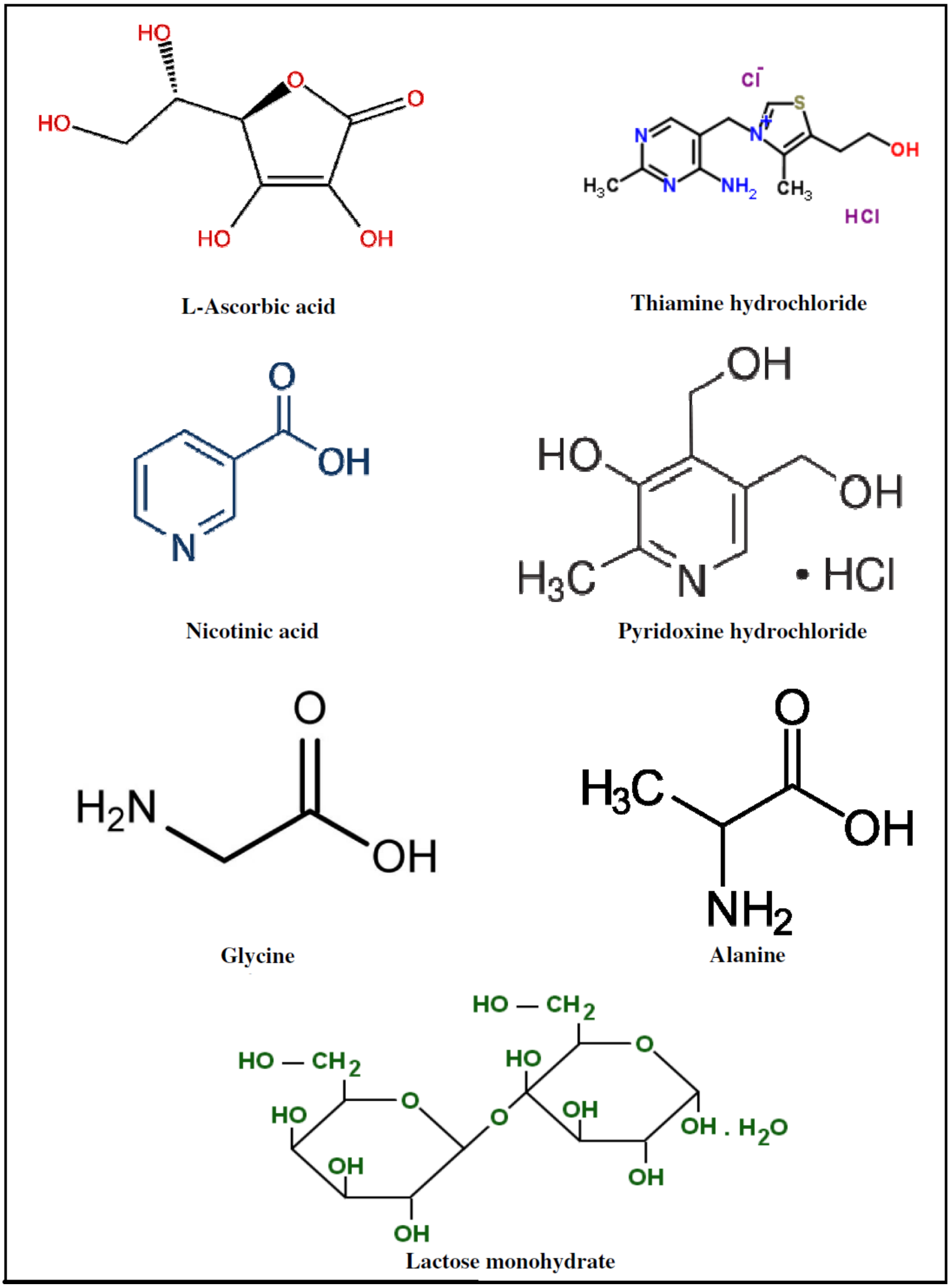

Fig. 1.4. Structures of used food additives as solutes and cosolutes.

Tetraalkylammonium salts are bulky in nature and can orient water molecules around themselves depending on their alkyl chain lengths [135-136]. Therefore, aqueous solution of tetraalkylammonium cations can stand as model systems for the study of hydrophobic hydration and salts like tetrabutylammonium hydrogen sulphate (TBAHS), an ion-pairing reagent [137], can provide information about the effect of different non-covalent interactions on the stabilities of vitamins.

Ionic liquids are salts in liquid states which are of utmost important due to their versatile uses in pharmaceutical industries, water recycling, cellulose processing and as green solvents [138-142]. As salt solutions have a large effect on the conformation and properties of proteins, it is very interesting to observe the interaction between amino acids and ionic liquids in aqueous solutions. In comparison with other ionic liquids phosphonium based ionic liquids are more stable, less toxic and less expensive [143-144]. So we have used tributylmethyl phosphonium methyl sulphate i.e.; $[P_{4,4,4,1}][CH_3SO_4]$ as ionic liquid.

Sodium malonate is an disodium salt of an organic acid of relatively high charge density, it has a very high solubility in water and likely behaves as a cosmotrope in water perhaps stabilizing protein structure as well as conform with water structure about the protein [145-146]. It is used to increase the reproducibility of crystals and improve resistance to physico-chemical shocks. It also acts as a good cryoprotectant.

Uracil is one of the four nucleobases in the nucleic acid of RNA. It helps the body to synthesize many enzymes necessary for cell functioning. It is also used as a allosteric regulator in the body. It can be used for drug delivery.

Glucose is the most important sugar in human metabolism [147]. Glucose is the primary fuel used by most cells in the body to generate the energy that is needed to carry out cellular functions. The adult brain neurons have the highest energy demand which is provided by the blood glucose but high blood sugar can cause damage to nerves, blood vessels, and organs. It can also lead to other serious conditions.

1.9.2. Solvents

We have used different aqueous media as solvent. One on the component of the solvent is water. Water is known as the universal solvent as it dissolves more substances than any other liquids. It has prime importance to life as most of the biological reactions and transportations are taken place in the presence of water, also the cell contains 85% of water in it. Water allows chemical reactions to take place because it allows dissolved chemicals to move around. Because of this, water is used as a solvent in many industries that make substances such as foods, medicines, fertilizers, paints, pesticides, adhesives and paper. It is also sometimes used as a solvent of mining. Salts like tetrabutylammonium hydrogen sulfate, silver sulphate; sodium malonate, ionic liquid like tributylmethyl phosphonium methyl sulphate; vitamins like ascorbic acid; RNA base like uracil and carbohydrate like glucose are used as co solutes with water in the solvent.

1.10. Method of Investigation

The phenomena of solute-solute, solute-solvent and solvent-solvent interactions are intriguing. It is desirable to explore these interactions using different experimental techniques. For physico-chemical investigation important methods of densitometry, viscometry, Ultrasonic Interferometry, refractometry and UV-visible spectroscopy were used in the research works embodied in this thesis. Thermodynamic properties of solutions are not only useful for estimation of feasibility of chemical reactions in solution but they also offer one of the better methods of investigating the theoretical aspects of solution structure. Thermodynamic properties like apparent molar volume, partial molar volume, partial molar expansibility, etc. obtained from density measurements are generally convenient parameters for interpreting solute-solute and solute-solvent interactions in solution. The apparent and partial molar volumes of electrolyte solutions have proved to be very useful tools in elucidating structural interactions (i.e., ion-ion or solute-solute ion-solvent or solute-solvent, and solvent-solvent interactions) occurring in solution. The viscosity of electrolyte and non-electrolyte solutions is another important parameter to study their solution behavior. The compressibility, a second derivative of Gibbs energy, is also a sensitive indicator of molecular interactions and can provide useful information in such cases where partial molar volume data alone cannot provide an unequivocal interpretation of these interactions. The temperature and concentration dependence of viscosities of electrolyte and non-electrolyte solutions help to understand ion-solvent or solute-solvent (solvation) and long-range ion-ion electrostatic interactions. The change in solvent viscosity by the addition of electrolytes is attributed to inter-ionic and ion-solvent effects. The viscosity *B*-coefficients gives a satisfactory interpretation of ion-solvent or solute-solvent interactions such as the effects of solvation, preferential solvation and long range structure-breaking or structure-making capacity of the solutes. Refractometric studies also render an insight into the different molecular interactions prevailing in solutions containing mixed solvent systems and helps in understanding of the behavior of the solutes with different solvents. In addition to these, UV-visible spectroscopy is used to support the results obtained from density, viscosity, ultrasonic sound velocity and refractive index measurements.

References

[1] A. L. Branen, P. M. Davidson, S. Salminen, J. H. Thorngate, Food Additives, 2nd ed. CRC Press, New York, 2001, ch.1.

[2] S. S. Aswale, S. R. Aswale, A. B. Dhote, J. Natural Sciences. 1 (2013) 13-19.

[3] S. P. Jengathe, S. S. Dhondge, L. J. Paliwal, V. M. Tangde, S. Mondal, J. Chem. Thermodyn. 87 (2015) 78-87.

[4] A. Pal, S. Soni, J. Chem. Engg. Data. 58 (2013) 18-23.

[5] A. Sarkar, B. Pandit, B. Sinha, J. Chem. Thermodyn. 98 (2016) 118-125.

[6] P. Mergenthaler, U. Lindauer, G. A. Dienel, A. Meisel, Trends Neurosci. 36(10) (2013) 587-597.

[7] L. Pellerin, Diabetes Metab. 36 (2010) doi: 10.1016/s1262-3636(10)70469-9.

[8] T. A. M. Masagati, Chemistry of Food Additives and Preservatives, Wiley-Blackwell, 2013, ch.1.

[9] B. Nayak, K. M. Nayer, Food Chemistry, 80 (2003) 545-550.

[10] M. S. Rahaman, Handbook of Food Preservation, 2nd ed. CRC Press, New York, 2007.

[11] S. S. Dhondge, P. N. Dahasahasra, L. J. Paliwal, D. W. Deshmukh, J. Chem. Thermodyn. 76 (2014) 16-23.

[12] X. Ren, C. Zhu, Y. Ma, J. Chem. Engg. Data 60 (2015) 1787-1802.

[13] H. D. Belitz, W. Grosch, P. Schieberle, Food Chemistry, 4th ed. Springer, Berlin, 2009

[14] T. Populin, S. Moret, S. Traunt, L. S. Conte, Food Chemistry 104 (2007) 1712-1717.

[15] D. B. MacDougall, Coloring of Food, Drugs, and Cosmetics. Marcel Dekker, Inc., New York, Basel, USA, 2009.

[16] M. Suman, G. Silva, D. Catelliani, U. Berisillini, V. Caffarra, M. Careri, J. Chromatography A 1216 (2009) 3758-3766.

[17] F. Hutteau, M. Mathlouthi, M. O. Protmad, D. Kilcast, Food Chemistry 63 (1) (1998) 9-16.

[18] X. Jang, C. Zhu, Y. Ma, J. Chem. Eng. Data 58 (2013) 2970-2978.

[19] T. S. Banipal, H. Singh, P. K. Banipal, V. Singh, Thermochimica Acta 553 (2013) 31-39.

[20] M N. Roy, K. Sarkar, A. Sinha, J. Solution. Chem. 43 (2014) 2212-2223.

[21] D. Rudan-Tasic, C. Klofutar, J. Horvat, Food. Chem. 86 (2014) 161-167.

[22] C. Klofutar, J. Horvat, D. Rudan-Tasic, Monatshefte. Fur. Chemie. 137 (2006) 1151-1162.

[23] G. Ayranci, M. Sahin, E. Ayranci, J. Chem. Thermodyn. 39 (2007) 1620-1631.

[24] S.S. Dhondge, D.W. Deshmukh, L.J. Paliwal, J. Chem. Thermodyn. 58 (2013) 149-157.

[25] T.S. Banipal, H. Singh, P.K. Banipal, V. Singh, Thermochim. Acta. 553 (2013) 31-39.

[26] T. S. Banipal, H. Singh, P. K. Banipal, V. Singh, Thermochimica Acta 553 (2013) 31-39.

[27] S. S. Dhondge, D. W. Deshmukh, L. J. Paliwal, J. Chem. Thermodyn. 58 (2013) 149-157.

[28] D. Ma, X. Jiang, G. Wei, C. Zhu, J. Chem. Engg. Data 60 (2015) 1279-1290.

[29] R. R. Naik, S. V. Bawankar, P. V. Tekade, O. A. Mahodaya, Russian J. Physical Chem. A 89(1) (2015) 152-158.

[30] T. S. Banipal, H. Singh, P. K. Banipal, Thermochimica Acta 572 (2013) 6-22.

[31] S. Cabini, G. Conti, E. Matteol, M.R. Tine, J. Chem. Soc. Faraday Trans. 77 (1981) 2377-2384.

[32] M. Iqbal, R.E. Verrall, J. Phys. Chem. 91 (1987) 967-971.
[33] A.K. Mishra, J.C. Ahulwalia, J. Phys. Chem. 88 (1984) 86-92.
[34] P. K. Banipal, A. K. Chahal, N. Hundal, T. S. Banipal, Carbohydrate Research 345 (2010) 2262–2271.
[35] L. M. P. Verissimo, V. C. M. Ribeiro, A. C. F. Ribeiro, M. Rodrigo, M. A. Esteso, Food Chemistry 163 (2014) 284-288.
[36] D. R. Tasic, C. Klofutar, Food Chemistry 84 (2004) 351-357.
[37] C. Klofutar, D. R. Tasic, J. Sol. Chem. 35 (2006) 395-406.
[38] G. L. Patrick, An introduction to medicinal chemistry, Oxford University press, New York, 1995.
[39] V. K. Sayal, S Chavan, P Sharma, J. Indian. Chem. Soc. 82 (2005) 602-607.
[40] A. C. F. Ribeiro, M. C. F. Barros, L. M. P. Verissimo, C. I. A. V. Santos, A. M. T. D. P. V. Cabral, G. D. Gaspar, M. A. Esteso, J. chem.. Thermodyn. 54 (2012) 97-99.
[41] A. Tromans, E. Konigsberger, P. M. May, G. Hefter, J. Chem. Eng. Data 50 (2005) 2019-2025.
[42] Z. Kinart, A. Bald, Phys. and Chem. of Liquids 49 (2011) 366-378.
[43] A. Chmielewska, A. W. Stasiewicz, A. Bald, J. Mol. Liquids 122 (2005) 110-115.
[44] G. R. Hedwig, G. B. Jameson, J. Chem. Thermodyn. 59 (2013) 188-194.
[45] H. Kumar, M. Singala, R. Jindal, Thermochimica Acta 571 (2013) 28-41.
[46] M. Singla, R. Jindal, H. Kumar, Thermochimica Acta 591 (2014) 140-151.
[47] M. Singal, R. Jindal, H. Kumar, J. Chem. Thermodyn. 76 (2014) 100-115.
[48] M. J. Iqbal, Q. M. Malik, J. Chem. Thermodyn. 37 (2005) 1347-1350.
[49] H. Shekaari, M. T. Z. Moattar, F. Ghaffari, J. Mol. Liquids 202 (2015) 86-94.
[50] T. S. Banipal, N. Kaur, P. K. Banipal, J. Chem. Thermodyn. 82 (2015) 12-24.
[51] R. Mehera, P. Yadav, Phys and Chem of Liquids 50 (2012) 88-101.
[52] A. E. Bell, W. M. J. Madgin, Chem. Soc. (1947) 74-76.
[53] S. Ryshetti, A. Gupta, S. J. Tangeda, R. L. Gardas, J. Chem. Thermodyn. 77 (2014) 123-130.
[54] S. P. Jengathe, S. S. Dhondge, L. J. Paliwal, V. M. Tangde, S. Mondal, J. Chem. Thermodyn. 87 (2015) 78-87.

[55] A. Pal, S. Soni, J. Chem. Engg. Data 58 (2013) 18-23.

[56] A. Sarkar, B. Pandit, B. Sinha, J. Chem. Thermodyn. 98 (2016) 118-125.

[57] H. Kumar, I. Behal, M. Singla, J. Chem. Thermodyn. 95 (2016) 1-14.

[58] S. Chauhan, K. Singh, M. S. Chauhana, A. Umar , C.N. Sundaresan, J. Mol. Liquids 214 (2016) 390-399.

[59] S. S. Dhondge, S. P. Zodape, D. V. Parwate, J. Chem. Thermodyn. 48 (2012) 207-212.

[60] K. Rajagopal, S. S. Jayabalakrishnan, J. Serb. Chem. Soc. 76(1) (2011) 129-142.

[61] S. Chauhan, K. Singh, K. Kumar, S. C. Neelakantan, G. Kumar, J. Chem. Engg. Data 61 (2016) 788-796.

[62] T. R. Aalto, M. C. Firman, N. E. Rigler, Journal of Pharmaceutical Science 2006, DOI: 10.1002/jps.3030420802.

[63] Y. J. Kim, Biol Pharm Bull. 30(6) (2007) 1052-1055.

[64] M. Strlic, T. Radovic, J. Agric. Food Chemistry 50 (2002) 6313–6317.

[65] L. O'Bruen-Nabors, R. C. Gelardi, Alternative Sweeteners: An Overview in Alternative Sweeteners, Maecer Dekker, New York, 2nd ed. 1991, pp 1-10.

[66] Merriam-Webster Online Dictionary, 2007, pp.12-19.

[67] A. Sarkar, B. Pandit, B. Sinha, J. Chem. Thermodyn. 96 (2016) 161-168.

[68] W.T. Keeton, J.L. Gould, Biological Science, 5th ed., W. W. Norton & Co, New York, 1993.

[69] A.R. Ravishankara. Science 276 (1997) 1058-1065.

[70] K. Ibuki, M. Nakahara J. Phys. Chem. 94 (1990) 8370-8373.

[71] A. Henni,. J.H. Jonathan. T. Paitoon, C. Amit, J. Chem. Eng. Data 48 (2003) 1062-1067.

[72] J. Burgess, Metal Ions in Solutions; Ellis Horwood, New York, 1978.

[73] C. Reichard, Solvents and Solvent Effects in Organic Chemistry, WILEY-VCH, 3rd edn, 2003.

[74] P.J. Suppan, J. Chem. Soc., Faraday Trans. 83 (1987) 495-509.

[75] P. Chatterjee, S.J. Bagchi, J. Chem. Soc. Faraday Trans. 87 (1991) 587-591.

[76] J.M. McDowali, C.A. Vincent, J. Chem. Soc. Faraday Trans. 1 (1974) 1862-1868.

[77] S.T. Osinska, A. Piekarska, J. Chem. Soc., Faraday Trans. 85 (1989) 3709-3715.

[78] V.K. Rattan, S. Kapoor, K. Tochigi. J. Chem. Eng Data 47 (2002) 1388-1390.

[79] H.S. Harned, B.B. Owen, The Physical Chemistry of Electrolytic Solutions, Reinhold, New York, 3rd ed., 1958.

[80] J.E. Gordon, The Organic Chemistry of Electrolyte Solutions, Wiley-Interscience, 1975.

[81] U. Mayer, V. Gutmann, Adv. Inorg. Chem. Radiochem. 17 (1975) 189-223.

[82] R.G. Pearson, Hard and Soft Acids and Bases, Dowdon, Hutchinson and Ross, Strondsburgh, 1973.

[83] J.Y. Choi, E.J. Park, S.H. Chang, T.J. Kang, Bull. Korean. Chem. Soc. 30 (2009) 1452-1458.

[84] D. J. Gordon, J.J. Balbach, R. Tycko, S.C. Meredith, J. Biophys. 86 (2004) 428-434.

[85] S.B. Prusiner, Proc. Natl. Acad. Sci. USA, 95(1998) 13363-13383.

[86] L. Onsager, J. Am. Chem. Soc. 58 (1936) 1486-1493.

[87] J.G. Kirkwood, J. Chem. Phys. 2 (1934) 351-361.

[88] J. Burgess, Metal Ions in Solution, Ellis Horwood, Chichester, 1978, Ch. 2, 5.

[89] Y. Marcus J. Phys. Chem. B 109 (2005) 18541-18549.

[90] W.E. Waghorne, Chem. Soc. Rev. (1993) 285-292.

[91] C. Klofutar, J. Horvat, D. R. Tasic, Acta Chim. Slov. 53 (2006) 274-283.

[92] S. K. Sharma, G. Singh, H. Kumar, R. Kataria, J. Chem. Thermodyn. 98 (2016) 214-230.

[93] A. K. Nain, J. Chem. Thermodyn. 98 (2016) 338-352.

[94] A. Apelblat, E. Manzurola, J. Chem. Therodyn. 98 (2016) 173-178.

[95] F. Shakeel, N. Haq, F. K. Alanazi, I. A. Alsarra, J. Mol. Liquids 219 (2016) 439-443.

[96] H. Xie, L. Zhao, C. Liu, Y. Cao, X. Lu, Q. Lei, W. Fang, J. Chem. Thermodyn. 99 (2016) 75-81.

[97] S. Ryshetti, N. Raghuram, E. J. Rani, S. J. Tangeda, Int. J. Thermophys. 43 (2016) 1-10.

[98] M. Jozwiak, L. Madej-Kiełbik, H. Piekarski, Thermochimica. Acta 533 (2012) 22-27.

[99] B.D. Djordjevic, I. R. Radovic, M.J. Kijevcanin, A. Ž. Tasic, S. P. Šerbanovic, J. Serb. Chem. Soc. 74 (2009) 477-491.

[100] M. Iqbal, R.E. Verral, Can. J. Chem. 67 (1989) 727-735.

[101] E.P. Georgios, I. Z. Ioannis, J. Chem. Eng. Data 37 (1992) 167-172.

[102] M. Almasi, Thermochimica. Acta 554 (2013) 25-31.

[103] A. Ali, A.K. Nain, J. Pure. Appl. Ultrasonics 22 (2000) 10-15.

[104] J.H. Dymond, Chem. Soc. Rev. 14 (1985) 317-356.

[105] J.F. Coetzee, W. R. Sharpe, J. Phys. Chem. 76 (1971) 3141-3148.

[106] R. Natarajan, P. Ramesh, J. Pure Appl. & Ind. Phys. 1(4) (2011) 252-258.

[107] M. Aravinthraj, S. Venkatesan, M. Kamaraj, Int. J. Chem. Enviorn. & Pharma. Res. 2(1) (2011) 5-11.

[108] R. T. Lagemann, W. S. Dunbar, J. Phys. Chem. 49 (1945) 428-436.

[109] S.D. Deosarkar, M.L. Narwade, V.V. Pandhare, Chem Sci Trans. 2 **(**2013) 37.

[110] P. Pacák, Chem. Papers. 43 (1989) 489-500.

[111] X. Jiang, C. Zhu, Y. Ma, J. Chem. Thermodyn. **71** (2014) 50-63.

[112] A. Sarkar, D. K. Mishra, B. Sinha, J. Sol. Chem. 45 (2016) 560-573.

[113] S. Gibson, Principles of Nutritional Assessment, Oxford University Press, New York, 1990.

[114] D. Lonsdale, Evid. Based Complement Alternate. Med. 3 (2006) 49-59.

[115] L. Bettendorff, M. Peeters, P. Wins, E. Schoffeniels, J. Neurochem. 60 (1993) 423-434.

[116] H. Horton, L. Moran, R. Ochs, J. Rawn, K. Scrimgeur, Principles of Biochemistry, Prentice Hall, 1996.

[117] C. A. Elvehjem, L. J. Teply, Chem. Rev. 33 (1943) 185-208.

[118] A. N. Nesmeyanov, N. A. Nesmeyanov, Fundamentals of Organic Chemistry, Vol. 3, Mir Publishers, Moscow, 1981, p. 393.

[119] A. S. Fauci, E. Braunwald, K. J. Isselbacher, J. D. Wilson, J. B. Martin, D. L. Kasper, S. L. Hauser, D. L. Long, Harrison's Principles of Internal Medicine, Vol. 1, 14th ed., McGraw- Hill, New York, 1998.

[120] J. Block, in Vitamins, Kirk-othmer Encylopedia of Chemical Technology, S. Seidel, Ed., Wiley, Hoboken, Vol. 25, 5th ed., 1996, p. 797.
[121] L. A. Carlson, J. Int. Med. 258 (2005) 94-114.
[122] A. Kundu, N. Kishore, J. Solution Chem. 32 (2003) 703-717.
[123] S. A. Denslow, A. A. Walls, M. E. Daub, Physiol. Mol. Plant Pathol. 66 (2005) 244-255.
[124] I. Kikic, N. D. Zordi, M. Moneghini, D. Solinas, J. Chem. Engg. Data 56 (2011) 4978-4983.
[125] I. N. A. Giri, S. Teshima, A. Kanawaza, M. Ishilawa, Penaeus Japonicas. Aquacalture 157 (1997) 263-275.
[126] R. Bhat, J. C. Ahluwalia, J. Phys. Chem. 89 (1985) 1099-1105.
[127] H. Zhao, Biophys. Chem. 122 (2006) 157-183.
[128] P. K. Banipal, V. Singh, N. Aggarwal, T. S. Banipal, Food Chemistry 168 (2015) 142-150.
[129] R. C. Hwang, G. R. Peck, Pharmaceutical Technology 25(6) (2001) 54-68.
[130] K. Zuurman, K. A. Riepma, G. K. Bolhuis, International Journal of Pharmaceutics 102 (1-3) (1994) 1-9.
[131] A. Bartolini, A. Ferrari, A. Ottani, S. Guerzoni, R. Tacchi, S. Leone, Paracetamol, CNS Drug Rev. 12 (2006) 250-275.
[132] L. J. Roberts, J. D. Morrow, in: J.G. Hardman, L. E. Limbird, A. G. Gilman (Eds), Goodman & Gilman's. The Pharmalogical Basis of Therapeutics, 10th ed.McGraw-Hill, New York, 2001.
[133] S. Budavari, M. J. O'Neil, A. Smith, P. E. Heckelman, J. R. Obenchain Jr., J. A. R. Gallipeau, M. A. D'Arecea, The Marck Index, An Encyclopedia of Chemicals, Drugs, and Bilologicals, 13th ed. Merck & Co. Inc., Whitehouse Station, NJ, 2001.
[134] H. Kumar, I. Behal, M. Singla, J. Chem. Thermodyn. 95 (2016) 1-14.
[135] M.N. Roy, B. Sinha, V.K. Dakua, Pak. J. Sci. Ind. Res. 49 (2006) 153-159.
[136] L.H. Blanco, E.F. Vargas. J. Solution. Chem. 35 (2006) 21-27.
[137] P. Jain, S. Sharma, R.K. Shukla, Phys. Chem. Liq. 51 (2013) 547-566.
[138] A. C. MacMillan, T. M. Mclntire, J. A. Freites, D. J. Tobias, S. A. Nizkorodov, J. Phys. Chem. B 116 (2012) 11255-11265.

[139] T. Welton, Chem. Rev. 99 (1999) 2071-2084.

[140] M. J. Earle, K. R. Seddon, Pure Appl. Chem. 72 (2000) 1391-1398.

[141] J. Dupont, R. F. De Souza, P. A. Z. Suarez, Chem. Rev. 102 (2002) 3667-3692.

[142] M. N. Roy, M. C. Roy, S. Basak, Int. J. Thermophys. 35 (2014) 853-864.

[143] C. M. S. S. Neves, P. J. Carvalho, M. G. Freire, J. A. P. Coutinho, J. Chem. Thermodyn. 43 (2011) 948-957.

[144] C. J. Bradaric, A. Downard, C. Kennedev, A. J. Robertson, Y. Zhou, Green Chem. 5 (2003) 143-152.

[145] K. D. Collins, P. N. A. S. 92 (1995) 5553-5557.

[146] A. Mcpherson, Protien Science. 10 (2001) 418-422.

[147] P. Mergenthaler, U. Lindauer, G. A. Dienel, A. Meisel, Trends Neurosci. 36(10) (2013) 587-597.