Volumetric and Viscometric Study of N-acetylcysteine in binary and ternary system

by

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A thesis submitted in partial fulfillment of the requirements for the degree of
M.Sc in Department of Chemistry

Khulna University of Engineering & Technology
Khulna-9203, Bangladesh
December, 2016.

Dedicated

To

The Scientists and people of Bangladesh

Declaration

This is to certify that the thesis work entitled **"Volumetric and Viscometric Study of N-Acetylcysteine in binary and ternary system"** has been carried out by **Utpal Kumar Gosh** in the Department of Chemistry, Khulna University of Engineering & Technology, Khulna, Bangladesh. The above thesis work or any part of this work has not been submitted anywhere for the award of any degree or diploma.

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Acknowledgement

I am extremely indebted to my respected supervisor Prof. Dr. Mohammad Abu Yousuf, Professor, Department of chemistry, Khulna University of Engineering and Technology, Khulna, for his careful guidance throughout the period of his dissertation.

I express sincere gratitude to my reverend teacher Bablu Hira Mondol, Asistant Professor, Department of chemistry, Jessore University of Science and Technology, Jessore, for his extreme encouragement, in every stage of my educative life.

Without their cooperation, invaluable suggestion, encouragement and constructive guidance, throughout this research work would have not been materialized. I will remember their inspiring guidance and cordial behavior forever in my future life.

I am pleased to express my gratitude to the Department Head Prof. Dr. Md Abdul Motin for providing me necessary laboratory facilities and proper guidance for the research.

I should take this opportunity to express my sincere thanks to all teacher of this department for their valuable advice and moral support in my research work.

I am highly grateful to the authority of KUET for giving the opportunity of research for the work.

I am also express my thanks to all the stuffs of this department especially Mr. Murad Ahmed.

I wish to thank my parents for their grate understanding and support.

(Utpal Kumar Gosh)

Abstract

Volumetric and viscometric studies of binary mixtures of ethanol–NAC (N-Acetylcysteine), water–NAC and ternary mixtures of ethanol–water–NAC were done. NAC have been investigated in binary and ternary systems over a concentration range of (1-18) % (w/v) at 298.15 to 323.15 K at 5 K intervals.

Densities of the binary systems, water–NAC and ethanol–NAC have been found to be increased with increasing concentration of NAC and decreased with increasing temperature. Densities of water–NAC have been found higher than that of ethanol–NAC system. On the other hand, in ternary system densities increased with the increasing ratio of water in ethanol–water mixtures. The densities of ternary system are higher than binary system.

The apparent molar volumes, $\boldsymbol{\varphi_v}$ of both binary and ternary mixtures were determined from the densities of the mixtures. The $\boldsymbol{\varphi_v}$ values have been found to be positive throughout the whole concentration range for NAC in ethanol, water and aqueous ethanol systems. The apparent molar volumes, $\boldsymbol{\varphi_v}$ of NAC in ethanol, water and aqueous ethanol were found to be increased with concentration at all temperatures. These results may be due to the solute–solvent, and solute–solute interaction through H-bond, dipole-dipole and $S\cdots S$ linkage in the solutions. $\boldsymbol{\varphi_v}$ values were found to be increased with increasing temperature at any concentration of the solution may be due to increased thermal agitation at higher temperatures. It may also be assumed as the concentration increases because solute–solute interactions by $S\cdots S$ linkage start to gain importance in addition to solute-solvent interactions. This shows that $\boldsymbol{\varphi_v}$ **v**alues are dependent upon concentration as well as the temperature.

The apparent molar volumes at infinite dilution ($\boldsymbol{\varphi_v^o}$**)** were computed by extrapolating $\boldsymbol{\varphi_v}$ values to zero concentration. The $\boldsymbol{\varphi_v^o}$ values provide information on solute–solvent interactions, as solute–solute interactions can be assumed to be eliminated at infinite dilution. The variations of both $\boldsymbol{\varphi_v^o}$ values with temperature were examined. $\boldsymbol{\varphi_v^o}$ Values were found to be increased with increasing temperature for all systems. Investigated systems showed small positive values for S_v which indicate that the solvation process involve strong interaction but not pure ionic. The apparent molar expansivities at

infinite dilution (φ_E^0) were found to be positive. Positive values indicate that, on heating some NAC molecules may be released from the solvation layer of ion.

Viscosity values, η of NAC in ethanol, water and aqueous ethanol were found to be increased with concentration at all five temperatures but decreased with the increase of temperature. The increase of η values of NAC with concentration can be attributed to the increase in both solute–solvent and solute–solute interactions with concentration as mentioned. At the same time, at a constant temperature and concentration, values of η are found to be increased with the ratio of the water in ethanol−water of ternary system but in binary system ethanol−NAC is higher than water−NAC viscosity because of larger molecule of ethanol.

The change of free energy values for viscous flow, ∆G* were found to be positive indicate that work has to be done to overcome the energy barrier for the flow process. The positive ∆H values indicate that work has to be done for all the investigated systems. That is, the viscous flow is not thermodynamically favored for the systems studied. The ∆S* values are positive for all the systems studied except ethanol–NAC system. This means that except ethanol–NAC system other binary and ternary systems are random that those of the pure one.

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Symbols/ Abbreviations	Explanation
K_d	Dissociation Constant
λ_i	Ionic conductance
η	Viscosity
λ_1^0	Limiting Ionic conductance
A	Area of contact between the two layers
f	Tangential force
ϕ	Fluidity
l	Length
Pa.S	Pascal-Second
cP	centipoise
mPa.S	Milli-Pascal-second
v	Velocity
r	Radius
P	Pressure
t	Flow time
ρ	Density of the liquid/solution
φ_v	Apparent molar volume
φ_E^0	Apparent molar expansivity at infinite dilution
ΔG*	Free energy
ΔH*	Change of Enthalpy and
ΔS*	Entropy
h	Difference in height of the surface of the two reservoirs
g	Acceleration due to gravity
NAC	N-Acetylcysteine
IUPAC	The International Union of Pure and Applied Chemistry

CHAPTER I

Introduction

1.1.1 The phenomena of solute-solvent interaction

Elucidation of the nature of ion-solvent interaction [1–2]and interpretation of the thermodynamic and transport processes in terms of such parameters as effective size of the solvated ions in solutions have been two of the most difficult problems in the understanding of electrolytic solutions. This is because there is not satisfactory model to represent the various phenomena that occur in solution and the incompleteness in the understanding of the structure of the liquids in general. There are a number of evidences of solvation of ions [1–2] or solute molecules a number of studies have discussed the effect of solvation on the equilibrium properties of liquids.

The process of solvation and the process of dissolution are known to be close related. When ionic crystal is added to a solvent, the electrostatic force of attraction between the oppositely charged ions in the crystal have to be overcome by interposing solvent layers around each of the ions. The ability of a solvent to dissolve a crystal is reflected by the following properties, its dielectric properties, polarity, degree of self-association and its ability to solvate. Studies on the phenomena of solvation have led to the conclusions that:

(i) The ionic compounds are moderately soluble in dipolar aprotic solvents of relatively high dielectric constant but are much more soluble in water and other hydroxylic solvents like methanol. A number of inorganic salts are dissociated in acetonitrile, which is otherwise known to solvate cations and anions rather poorly [3].

(ii) The dielectric constant alone is not an adequate measure of solvating ability and may even play a major role in determining the solvation of ionic species. Cations should be better solvated in solvents having atoms with an unshared electron pair like nitrogen and oxygen. The cations have been found to be strongly solvated in highly polar solvents with the negative charge localized on an oxygen atom, e.g. in sulphur dioxide, dimethylsulfoxide, phosphorus oxide, dimethylformamide [4]. Potassium iodide is less soluble than sodium iodide in methanol or water [5], but in dimethylsulfoxide or dimethylformamide the reverse is true, which could be due to differences of cation solvation.

The anions have been found to be solvated in two ways:

(i) Small ions are mostly solvated by hydrogen bonding which is superimposed upon solvation by ion-dipole interactions, and

(ii) Large ions are solvated by interaction due to mutual polarizability of the anions and the solvent superimposed upon solvation by dipole interactions. Thus while the anions are more strongly solvated in hydrogen bonding solvents than in dipolar aprotic solvents, the cations are better solvated in the latter type of solvents.

The solubility of halides in various solvents generally follows the order:

Iodides> bromides > chlorides > fluorides.

The alkaline halides are more soluble in hydroxylic solvents than in the dipolar aprotic solvents like acetonitrile and acetone. These are found to be more soluble in acetonitrile than in acetone [6].Electrolytes may be divided into two categories: ionophores and ionogens. While the former are ionic in character in the crystalline state as well as in the fused state and in highly dilute solutions, the latter have molecular crystal lattice and ionize in solution only if suitable interaction occurs with the solvent molecules.

The ionophores may exist in solution as an equilibrium mixture containing ion-pairs and free ions [7].

$$\underset{\text{solvated}}{M^+X^-} \rightleftharpoons \underset{\text{solvated}}{M^+} + \underset{\text{solvated}}{X^-}$$

The ion-pairs are of oppositely charged ions having life terms sufficiently long to be recognized as kinetic entities in solution and in which only electrostatic forces are assumed [1]. Fuoss *et al*. [8] have studied intensely the dependence of the dissociation constant, K_d, on the dielectric constant, the temperature and the nature of the salt. It was found to be large for solvents having high dielectric constant. It has also been found to be dependent on the distance of closest approach of the ions in the ion pairs. For hydroxylic solvents, large ions have larger K_d values and lower conductance values than smaller ions, which doesn't hold for other solvents.

Interaction of the ions with the solvent molecules causes low conductance. Na^+ ion behaves as a large ion as the K_d of iodides of Bu_4N^+ and Na^+ are found to be of the same order. Small ions like Li^+, F^- have low conductance in acetone [9] but have low K_d values which have been attributed to the loss of the solvent molecules from the ion-pairs [9]. Solute-solvent interactions have been studied in details by various methods; some important ones may be listed as follows:

- (i) Study of the solute-solvent interactions through transference experiments.
- (ii) The effect of solvation on the ionic conductance.
- (iii) The experiments applying stoke's law and their relevance to the nature of solvation.
- (iv) Polarographic measurements of solutions.
- (v) The spectral results due to the presence of the ions in solutions.

A relationship between the values of the limiting equivalent ionic conductance, λ_i and the viscosity, η value was advocated and utilized by Walden and others to study the solute-solvent interactions [10]. In one approach which assumes the constancy of the product $\lambda_i\eta$ the effects of variation of temperature, viscosity and variation of the solvent were studied. For large organic ions [10], the temperature co-efficient was found to be nearly constant in water as well as other non-aqueous solvents, while for the other ions it showed variations. For changing solvents, the product was found to vary widely in the case of inorganic ions which have been interpreted to be due to differences in solvation numbers of the ion in the various solvents. In another approach to this study Pure and Sherrington [11] used the relation between viscosity η_t, and limiting ionic conductance λ_i^0, to measure the radii of interaction of solvent and solute, called stoke's law radii, r. They compared the crystallographic radii of some cations and anions with stoke's law radii in the case of dimethylamide and dimethylsulphoxide solvents. They found the degree of solvation to decrease from lithium to cesium and to be less for silver and ammonium ions which have nearly comparable crystallographic radii. They postulated the anions to be unsolvated in dipolar aprotic solvents as the radii obtained are of the same order as that of the crystallographic radii, and that the negative end of the dipole in the solvent molecule is unshielded while the positive end is protected by two methyl groups, so that the cations, but not the anions are solvated by these solvents. Volumetric and viscometric measurement provides valuable tool for the determination of interaction among solutes and solvents.

1.1.2 Viscosity

Viscosity means viscous ability. Simply, viscosity of a material is resistance to flow. The internal friction which opposes the relative motion of the adjacent layers of a fluid causes for the resistance to flow. When a fluid is flowing through a cylindrical tube, this internal friction arises because of intermolecular friction. Molecules are a slower moving layer try to decrease the velocity of the molecules in a faster moving layer and vice versa.

Viscosity is really a frictional effect experienced by one layer of a liquid in moving past another in much the same way as an object experiences frictional resistance when dragged on a surface. The friction force, f, resisting the flow of one layer of fluid past the adjacent layer is proportional to the area, A, of the interface between the layers and to$\frac{du}{dr}$, the velocity gradient. This is Newton's law and is given by

$$f = \eta A \frac{du}{dr}$$

Where η (eta, a Greek letter), the constant of proportionality, is called the co-efficient of viscosity. When the velocity gradient is unity and the area is 1 sq-cm, η is equal to the force; or the co-efficient of viscosity,η may be defined as the force per 1 sq-cm required to maintain a difference of velocity of 1 cm per second between two parallel layers 1 cm apart. The reciprocal of theco-efficient of viscosity is known as the fluidity, ∅, or

$$\varnothing = \frac{1}{\eta}$$

Fluidity is a measure of the ease with which a liquid can flow. The connection between these quantities was first derived by J. L. M. Poiseuille in 1844, known as the Poiseuille equation [12]. If a liquid with a coefficient of viscosity (η) flows with a uniform velocity, at a rate of v cm^3 in t seconds through a narrow tube of radius r cm, and length 1 cm under a driving pressure of P dynes cm^{-2} then [12]:

$$\eta = \frac{\pi P r^4 t}{8 l v} \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots (1.1.1)$$

This equation known as Poiseuille's equation holds accurately for stream-line flow but not for the turbulent flow which sets as higher velocities.

Where, η is a proportionality constant, known as the coefficient of viscosity or simply viscosity of the liquid. The CGS unit of viscosity i.e., dynes sec cm^{-2} = g $cm^{-1}sec^{-1}$ is called poise, in honor of J.L.M. Poiseuille who is the pioneer in the study of viscosity. The SI unit of viscosity is the Pascal-second (Pa.S). Since viscosity of liquid is usually very small, it is usually expressed in millipoise (mP) or centipoise (cP) or mPa.S.

1.1.3 Factors affecting viscosity

Viscosity is first and foremost function of material. Most ordinary liquids have viscosities on the order of 1 to 1000 mPa·s, while gases have viscosities on the order of 1 to 10µPa·s. Pastes, gels, emulsions, and other complex liquids are harder to summarize. Some fats like butter or margarine are so viscous that they seem more like soft solids than like flowing liquids.

Temperature: The viscosity of a simple liquid decreases with increasing temperature (and vice versa). As temperature increases, the average speed of the molecules in a liquid increases and the amount of time they spend "in contact" with their nearest neighbors decreases. Thus, as temperature increases, the average intermolecular forces decrease. The exact manner in which the two quantities vary is nonlinear and changes abruptly when the liquid changes phase.

Pressure: Viscosity is normally independent of pressure, but liquids under extreme pressure often experience an increase in viscosity. Since liquids are normally incompressible, an increase in pressure doesn't really bring the molecules significantly closer together. Simple models of molecular interactions won't work to explain this behavior and, to my knowledge, there is no generally accepted more complex model that does. The liquid phase is probably the least well understood of all the phases of matter.

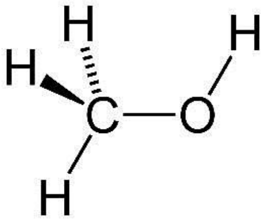
While liquids get runnier as they get hotter, gases get thicker. The viscosity of gases increases as temperature increases and is approximately proportional to the square root of temperature. This is due to the increase in the frequency of intermolecular collisions at higher temperatures. Since most of the time the molecules in a gas are flying freely through the void, anything that increases the number of times one molecule is in contact with another will decrease the ability of the molecules as a whole to engage in the coordinated movement. The more these molecules collide with one another, the more disorganized their motion becomes.

Cohesive forces: Cohesive forces are the intermolecular forces (such as those from hydrogen bonding and Van der Waals forces) which cause a tendency in liquids to resist separation. These attractive forces exist between molecules of the same substance. For instance, rain falls in droplets, rather than a fine mist, because water has strong cohesion which pulls its molecules tightly together, forming droplets. This force tends to unite molecules of a liquid, gathering them into relatively large clusters due to the molecules' dislike for its surrounding. The materials having stronger cohesive forces normally exhibit lower viscosities and vice-versa.

Adhesive force: Adhesive forces are the attractive forces between unlike molecules. They are caused by forces acting between two substances, such as mechanical forces (sticking together) and electrostatic forces (attraction due to opposing charges). In the case of a liquid wetting agent, adhesion causes the liquid to cling to the surface on which it rests. When water is poured on clean glass, it tends to spread, forming a thin, uniform film over the glasses surface. This is because the adhesive forces between water and glass are strong enough to pull the water molecules out of their spherical formation and hold them against the surface of the glass, thus avoiding the repulsion between like molecules. The materials having stronger adhesive forces normally reveal higher viscosities and vice-versa.

1.1.4 Properties of alcohol

In chemistry, an alcohol is any organic compound in which a hydroxyl group (–OH) is bound to a carbon atom of an alkyl or substituted alkyl group. It is composed of carbon, oxygen, and hydrogen and the general formula for a simple acyclic alcohol is $C_nH_{2n+1}OH$where n=1, 2, 3, etc. The saturated carbon chain is often designated by the symbol R, so that ROH can represent any alcohol in the homologous series. The –OH group bonded to sp^3hybridized carbon as shown above. It can therefore be regarded as a derivative of water, with an alkyl group replacing one of the hydrogen. The oxygen in an alcohol has a bond angle of around 109° (c.f. 104.5° in water), and two non-bonded electron pairs.



The properties of any given aliphatic alcohol depend on the nature of the alkyl group in the molecule and on the properties of the hydroxyl group. Generally, alcohols are clear, volatile and burn (oxidize) easily. Alcohols react with organic acids to form Esters. The reaction proceeds slowly but the rate of esterification is increased by the presence of hydrogen ions, which act as a catalyst in the reaction. Alcohols are very weak acids, intermediate in strength between acetylene and water. They undergo substitution with strongly electropositive metals such as sodium. Alcohols react with phosphorus pentachloride, when the hydroxyl group is replaced by a chlorine atom.

No gaseous alcohols are known at standard laboratory temperature. The lower members of the homologous series of aliphatic alcohols (containing C_1 to C_{10}) are clear colorless liquids at room temperature. They have varying solubility in water, the higher alcohols being less soluble. The alcohols higher than C_{12} are solids and are insoluble in water. Methanol, ethanol and propanol are miscible with water. The alcohols are miscible in all proportions with most organic liquids. The boiling points of the straight chain alcohols increase as the number of carbon atoms in the molecule increase. For a given molecular mass, there is a decrease in the boiling point when branching of carbon atoms occurs. Thus, the primary alcohols boil at a higher temperature than the secondary alcohols of the same molecular mass, and similarly, secondary alcohols have higher boiling points than the tertiary alcohols. The boiling points are much higher than is to be expected from their molecular masses. Hydrogen bonds alcohols associate neighboring molecules causes the boiling points high. These intermolecular bonds are considered to be intermediate in strength between weak Van der Waals forces and the strong forces between ions. The extra energy required to break the hydrogen bonds leads to an increase in boiling point.

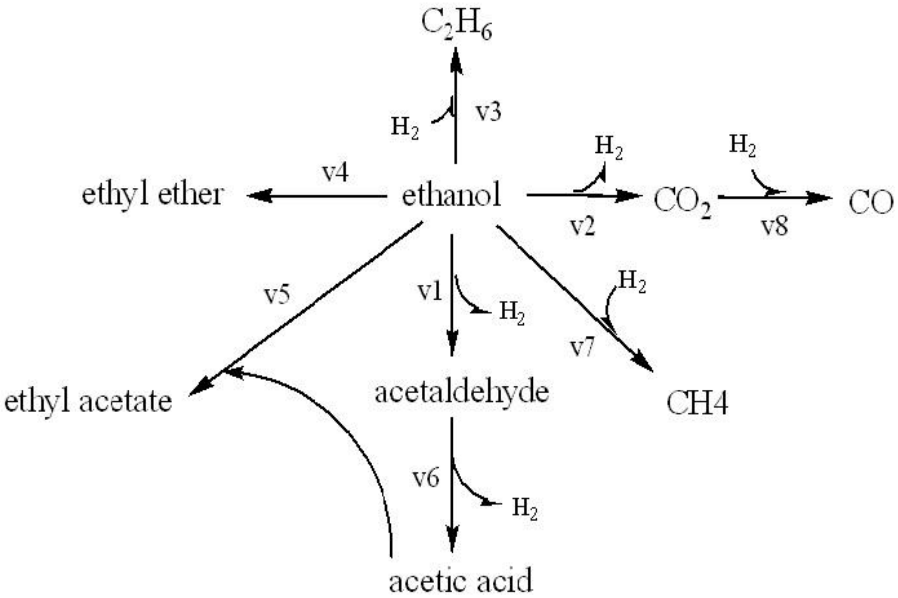
The hydroxyl group is referred to as a hydrophilic group, as it forms hydrogen bonds with water and enhances the solubility of alcohol in water. Methanol, ethanol, propanol, etc. are all miscible with water. Alcohols with higher molecular masses tend to be less water-soluble, as the hydrocarbon part of the molecule, which is hydrophobic ("water-hating"), in nature. In this thesis, Ethanol was used as solvent to find out the interaction of N-Acetylcysteine from the point of view of biological interests. Some of ethanol properties are listed in Table1.1.

Table 1.1: Some properties of Ethanol

Property	**Data**
Chemical Name	Ethanol
Chemical formula	C_2H_5OH
Appearance	Colorless liquid
Molecular mass	46.07 g mol^{-1}
Melting point	- 114 °C
Boiling point	78.37°C
Density	0.789 g.cm^{-3}
Viscosity	1.2 mPa.S (at 20 °C)
Vapor pressure	5.95 kPa (at 20 °C)
Solubility	Soluble in water

Ethanol shows the normal reactions of a primary alcohol. Thus it can be converted to alkyl halides; for example red phosphorus and iodine produce ethyl iodide, while PCl_3 with catalytic $ZnCl_2$ gives ethyl chloride. Reaction with acetic acid in the presence of an H_2SO_4 catalyst under Fischer esterification conditions gives ethyl acetate, while refluxing ethanol overnight with formic acid alone can produce ethyl formate. Oxidation of ethanol with $Na_2Cr_2O_7$ and H_2SO_4 gives only a yield of Ethanaldehyde, and therefore for this type of reaction higher yielding methods using PCC or the Swern oxidation are recommended. Oxidation with chromic acid yields Ethanoic acid. Ethanol is not only the oldest synthetic organic chemical used by man, but it is also one of the most important solvent. In industry ethanol is widely used as a solvent and a medium for chemical reactions. In addition, it is an important raw material for synthesis.

Some common reaction schemes of ethanol have given below:



1.1.5 Properties of Water

Water has a very simple atomic structure. The nature of the atomic structure of water causes its molecules to have unique electrochemical properties. The hydrogen side of the water molecule has a slight positive charge. On the other side of the molecule a negative charge exists. This molecular polarity causes water to be a powerful solvent and is responsible for its strong surface tension.

When the water molecule makes a physical phase change its molecules arrange themselves in distinctly different patterns. The molecular arrangement taken by ice (the solid form of the water molecule) leads to an increase in volume and a decrease in density. Expansion of the water molecule at freezing allows ice to float on top of liquid water.

1.1.5.1 Structure of water

It has been recognized that water is an ‘anomalous’ liquid many of its properties is differ essentially from normal liquids of simple structures [13]. The deviations from regularity indicate some kind of association of water molecules. The notable unique physical properties exhibited by liquid water are [14] : i) negative volume of melting ii) density maximum in normal liquid range (at $4\,^{0}$C) iii) isothermal compressibility minimum in the normal liquid range at ($46\,^{0}$C) iv) numerous crystalline polymorphs v) high dielectric constant vi) abnormally high melting, boiling and critical temperatures for such a low molecular weight substance that is neither ionic nor metallic vii) increasing liquid fluidity with increasing pressure and viii) high mobility transport for H^{+} and OH^{-} ions pure water has a unique molecular structure. The O-H bond length is 0.096 nm and the H-O-H angle 104.5^{0}. For a very long time the physical and the chemist have pondered over the possible structural arrangements that may be responsible for imparting very unusual properties to water. To understand the solute water interaction the most fundamental problem in solution chemistry the knowledge of water structure is a prerequisite. The physico-chemical properties of aqueous solution in most of the cares are interpreted in terms of the structural change produced by solute molecules. It is recognized that an understating of the structural changes in the solvent may be crucial to study of the role of water in biological systems. Various structural models that have been developed to describe the properties of water may generally be grouped into two categories, namely the continumm model and the mixture models. The continumm models [15, 16] treat liquid water as a uniform dielectric medium, and when averaged over a large number of molecules the environment about a particular molecules is considered to be the same as about any other molecules that is the behavior of all the molecules is equivalent. The mixture model theories [17, 18 and 19] depict the water as being a mixture of short lived liquid clusters of varying extents consisting of highly hydrogen bonded molecules which are mixed with and which alternates role with non bonded monomers. Among the mixture models, the flickering cluster of Frank and Wen [20], later developed by Nemethy and scherage [15], is commonly adopted in solution chemistry. Properties of dilute aqueous solutions in terms of structural changes brought about by the solutes can be explained more satisfactorily using this model than any other model. According to this model the tetrahedraly hydrogen bonded clusters, referred to as bulky water $(H_2O)_b$, are in dynamic equilibrium with the monomers, referred to as dense water, $(H_2O)_d$ as represented by [19].

$$(H_2O)_b \rightleftharpoons (H_2O)_d$$

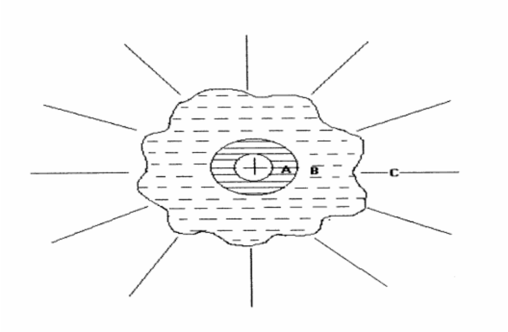


Fig 1.1: Frank and Wen model for the structure modification produce by an ion

The hydrogen bonding in the clusters is postulated [21] to be cooperative phenomenon. So when one bond forms several other also come into existence will be dissolved. The properties of solution can be accounted for in terms of solvent-solvent, solvent-solute and solute-solute interaction. In terms of thermodynamics, the concentration dependence of a given property extrapolated to the limit of infinite dilution provides a measure of solute-solvent interactions. Solute-water interaction or hydration phenomenon can be conveniently classified into three basic types:

i. Hydrophilic Hydration
ii. Ionic hydration
iii. Hydrophobic hydration

The introduction of a solute into liquid water produces changes in the properties of the solvent which are analogous to these brought about by temperature or pressure. The solute that shifts the equilibrium to the left and increase the average half-life of the clusters is termed as structure maker whereas that which has an effect in the opposite direction is called 'Structure breaker. The experimental result on various macroscopic properties provides useful information for proper understanding of specific interactions between the components and the structure of the solution. The thermodynamic and transport properties are sensitive to the solute-solvent, solute-solute, and solvent-solvent interaction. In solution systems these three types of interaction are possible but solute-solute interaction are negligible at dilute solutions. The concentration dependencies of the thermodynamic properties are a measure of solute-solute interaction and in the limit of infinite dilutions these parameters serve as a measure of solute-solvent interactions. The solute induced changes in water structure also result in a change in solution viscosity.

1.1.5.2 Hydrophilic hydration

Solvation occurs as the consequences of solute-solvent interactions different from those between solvent molecules themselves. The solubilization of a solute molecule in water is characterized by changes in the water structure that depend on the nature of the solute. Dissolution of any solute will disrupt the arrangement of water molecules in the liquid state and create a hydration shell around the solute molecule. If the solute is an ionic species, then this hydration shell is characterized to extend from an inner layer where water molecules near the charge species are strongly polarized and oriented by the electrostatic field, through an intermediate region where water molecules are significantly polarized but not strongly oriented, to an outer solvent region of bulk water where the water molecules are only slightly polarized by the electric field of the ion [22].

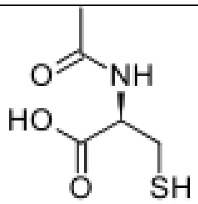
1.1.5.3 Hydrophobic hydration and hydrophobic interaction

The hydrophobic effect refers to the combined phenomena of low solubility and the entropy dominated character of the solvation energy of non-polar substances in aqueous media [23]. It is also reflected by anomalous behavior in other thermodynamic properties, such as the partial molar enthalpies, heat capacities, and volumes of the nonpolar solutes in water. This effect originated from as much stronger attractive interaction energy between the nonpolar solutes merged in water than their van der waals interaction in free space [24]. The tendency of relativity nonpolar molecules to “stick together” in aqueous solution is denoted as the hydrophobic interaction [25]. It results from hydrophobic hydration of a nonpolar molecule. Because hydrophobic hydration plays an important role in facilitating amphiphiles to aggregates in the aqueous bulk phase and to absorb, excessively, at the aqueous solution/air interface, it has been an ongoing objective of chemists working in these areas to seek a clearer understanding of the molecular nature behind the subtle hydration phenomenon occurring between nonpolar solutes and water. A brief but detailed account of the general aspects of hydrophobic hydration, which is essential to the rationalization of the results obtained in this work, is given at this point.

1.1.6 N-Acetylcysteine

N-Acetyl-L-cysteine (NAC), the preacetylysed form of simple amino acid cysteine, a synthetic precursor of cysteine and reduced glutathione has been in clinical use for more than 40 years. It is a powerful intracellular antioxidant, antitoxin improves immunity. NAC is a thiol compound which is also called Acetylcysteine, is an amino acid with the molecular formula $C_5H_9NO_3S$, Molar mass of acid 163.195 g/mole .The melting point and boiling point of NAC are 106 °C (223 °F) and 108 °C (226 °F) respectively. It is a white crystalline powder with a slightly acidic odor and characteristic sour tasting. It is a solid at room temperature, but melts easily with water, 4ml ALC; practically insoluble in chloroform and ether. The vapor pressure of NAC is estimated 1.1×10^{-5} mm Hg at 25 °C and stable of Stable in ordinary light; stable at temperature up to 120 °C; nonhygroscopic (oxidizes in moist air). The pH of NAC is 2 to 2.75 (1 in 100 ml) and dissociation constants pKa= 3.24 (carboxylic acid moiety) and Spectral Properties is Specific optical rotation: +5 °C at 20 °C (concentration = 3 g/100 mL). NAC is not found naturally in food sources; however cysteine is present in most high protein foods. NAC converts into cysteine. Cysteine is a nonessential amino acid produced by the body. Cysteine is primarily found in animal protein, along with the other ten essential amino acids. Meats such as pork, chicken, sausage, turkey and duck all contain the amino acid cysteine. Fish and lunch meats also contain cysteine. Dairy sources of cysteine include ricotta cheese, cottage cheese, yogurt and eggs. Cysteine can be found in some plant sources plant sources for vegetarians and vegans. Cysteine is found in granola and oat flakes. Vegetables like broccoli, red pepper and onion are significant sources of cysteine. Other plant sources include bananas, garlic, soy beans, linseed and wheat germ. Cysteine is important amino acid, but deficiency is relatively rare. Low levels of cysteine can cause slow growth in children and lowered immunity. Muscle loss, weakness, apathy and liver damage may also be a result of low

Table 1.2: Some properties of N-Acetylcysteine

Property	**Data**
Chemical Name	N-Acetylcysteine
Chemical formula	$C_5H_9NO_3S$
Chemical structure	
Appearance	white crystalline powder
Molecular mass	163.195 g/mole
Melting point	109 to 110 °C
Boiling point	407.7 °C at 760 mmHg
pH	2 to 2.75 (1 in 100 ml)
Density	1.294 g/cm^3
Flash Point	200.4 °C

cysteine in the diet. N-Acetylcysteine is a therapeutic medicine frequently used as a mucolytic agent and for treating acetaminophen hepatotoxicity. It increases the cell reserves of free radicals and acts as an antioxidant. It also inhibits the replication of HIV and prevents apoptosis in neurons. NAC prevents endotoxin-induced degeneration of oligodendrocyte progenitors and hypomyelination in developing rat brain. NAC may have a direct chelating effect on lead asseen by lowered serum lead levels. It prevents lead toxicity and reduces oxidative sequel of lead exposure. NAC crosses cell membranes and is rapidly consumed in producing intracellular glutathione. By reducing extracellular cysteine to cysteine, it acts as a source of SH groups and it can stimulate glutathione synthesis enhance glutathione-S–transferase activity promote detoxification and act directly on reactive oxidant radicals. NAC corrects the reduction in glutathione concentration and results in significant preservation of fluidity of membranes and of the activities of catalase, mitochondrial superoxide dismutase and different forms of glutathione peroxidase in biliary obstructed rats. NAC is a powerful scavenger of hypochlorous acid and is capable of reducing hydroxyl radicals and hydrogen peroxide. SH groups are essential for defence against reactive oxygen species. NAC can also prevent apoptosis caused by oxidative stress and promote cell survival by activating signal regulating pathways. With enormous medicinal and biological applications of NAC in human body, its solution behavior was investigated in versatile used water, in common organic solvent ethanol and also in water + ethanol mixed solvents as well that wasn’t done before to the best of my knowledge.

Theoretical Background

1.2.1 Physical Properties and chemical constitutions

In interpreting the composition, the structure of molecules and the molecular interaction in the binary and ternary systems, it is inevitable to find out the size and the shape of the molecules and the geometry of the arrangement of their constituent atoms. For this Purpose the important parameters are bond lengths or interatomic distance and bond angles. The type of atomic and other motions as well as the distribution of electrons around the nuclei must also be ascertained; even for a diatomic molecule a theoretical approach for such information would be complicated. However, the chemical analysis and molecular mass determination would reveal the composition of the molecules, and the study of its chemical properties would unable one to ascertain the group or sequence of atoms in a molecule. But this cannot help us to find out the structures of molecules, as bond length, bond angles, internal atomic and molecular motions, polarity etc. cannot be ascertained precisely.

For such information it is indispensable to study the typical physical properties, such as absorption or emission of radiations, refractivity, light scattering, electrical polarization, magnetic susceptibility, optical rotations etc. The measurement of bulk properties like, density, surface tension, viscosity etc. are also have gained increased importance during the recent years, because not only of their great usefulness in elucidating the composition and structure of molecules, but also the molecular interaction in binary and ternary systems.

The various physical properties based upon the measurement of density, viscosity, surface tension, refractive index, dielectric constant etc., have been found to fall into the following four categories [26].

(i) **Purely additive properties:** An additive property is one, which for a given system, is the sum of the corresponding properties of the constituents. The only strictly additive property is mass, for the mass of a molecule is exactly equal to the sum of the masses of its constituent atoms, and similarly the mass of a mixture is the sum of the separate masses of the constituent parts. There are other molecular properties like molar volume, radioactivity etc. are large additive in nature.

(ii) **Purely constitutive properties:** The property, which depends entirely upon the arrangement of the atoms in the molecule and not on their number is said to be a purely constitutive property. For example, the optical activity is the property of the asymmetry of the molecule and occurs in all compounds having an overall asymmetry.

(iii) **Constitutive and additive properties:** These are additive properties, but the additive character is modified by the way in which the atom or constituent parts of a system are linked together. Thus, atomic volume of oxygen in hydroxyl group (–OH) is 7.8 while in ketonic group (=CO) it is 12.2.The molar refraction, molecular viscosity etc. are the other examples of this type.

(iv) **Colligative properties:** A colligative property is one which depends primarily on the number of molecules concerned and not on their nature and magnitude. These properties are chiefly encountered in the study of dilute solutions. Lowering of vapor pressure, elevation of boiling point, depression of freezing point and osmotic pressure of dilute solutions on the addition of non-volatile solute molecules are such properties.

1.2.2 Molarity

Molarity (C), is defined as the number of moles of solute per liter of solution. If n is number of moles of solute and V liters is the volume of the solution then,

$$Molarity(C) = \frac{Number\ of\ moles\ of\ solute}{Volume\ of\ solution}$$

$$or\ C = \frac{n}{V} \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots \ (1.2.1)$$

The unit of molarity is mol.L^{-1}.

1.2.3 Molar volume of Mixtures

The volume in mL occupied by 1 mole of any substance is called the molar volume. On the other hand, if ρ is the density and M be the molar mass, molality (m) of a solution is defined as the number of moles of the solute per 1000 g of solvent. Mathematically,

$$Molality\ (\mathrm{m}) = \frac{\text{Number of moles of solute}}{\text{Weight of solvent in gram}} \times 1000$$

$$\text{or, } \mathrm{m} = \frac{\frac{\mathrm{a}}{\mathrm{M_2}} \times 1000}{\text{Volume of solvent in mL.} \times \text{density of solvent in g cm}^{-3}}$$

$$\text{or, m} = \frac{\mathrm{a}}{\mathrm{M_2}} \times \frac{1000}{\mathrm{V_1} \times \rho_0} \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots \text{(1.2.2)}$$

Where, a = weight of solute in gram.

M_2 = molecular weight of solute in gram.

V_1 = volume of solvent in mL.

ρ_0 = density of solvent in g.cm^{-3}.

Specific volume, (V) = $\frac{1}{\rho}$ mLg^{-1} ……………………………………………… (1.2.3)

Molar volume, (V_m) = $\frac{M}{\rho} m\ Lmol^{-1} \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots$ (1.2.4)

When two components are mixed together, there may be either a positive or a negative deviation in volume. One of cause of positive deviation in volume i.e. volume expansion has been explained by the disruption of the mode of association through H–bonding of liquids. The negative deviation in molar volume i.e. volume contraction has been thought of by many observers, as arising from the

I. compound formation through association
II. decrease in the intermolecular distance between the interacting molecules
III. interstitial accommodation of smaller species in the structural network of the larger species and
IV. change in the bulk structure of either of the substance forming the mixture.

1.2.4 Apparent molar volume

The apparent molar volume of a solute in solution, generally denoted by is defined by φ_v the relation [27]

$$\varphi_v = \frac{V - n_1 \overline{V}_1^{0}}{n_2} \quad \cdots\cdots (1.2.5)$$

Where, V is the volume of solution containing n_1 moles of solvent and n_2 moles of solute and $\overline{V}_1^{0}$ is the molar volume of the pure solvent at specified temperature and pressure. For binary solution, the apparent molar volume (φ_v) of an electrolyte in an aqueous solution is given by [28],

$$\varphi_v = \frac{1}{n_2}\left[\frac{n_1 M_1 + n_2 M_2}{\rho} - n_1 \overline{V}_1^{0}\right] \quad \cdots\cdots (1.2.6)$$

Where, $V = \frac{n_1 M_1 + n_2 M_2}{\rho}$ and

n_1 and n_2 are the number of moles, M_1 and M_2 are molar masses of the solvent and solute respectively and ρ is the density of the solution. For molar concentration, $n_2 = m$, the molality and n_1, the number of moles of solvent in 1000g of solvent, the equation for apparent molar volume takes the form [28,29],

$$\varphi_v = \frac{1}{m}\left[\frac{1000 + mM_2}{\rho} - \frac{1000}{\rho_0}\right]$$

$$\text{or, } \varphi_v = \left[\frac{M_2}{\rho} - \frac{1000(\rho - \rho_0)}{m\rho\rho_0}\right] \quad \cdots\cdots (1.2.7)$$

$$\text{or, } \varphi_v = \frac{1}{\rho}\left[M_2 - \frac{1000}{m}\left(\frac{W - W_0}{W_0 - W_e}\right)\right] \quad \cdots\cdots (1.2.8)$$

where, ρ_o and ρ are the densities of the solvent and solution and W_e, W_o and W are the weight of empty specific gravity bottle (pycnometer), weight of pycnometer with solvent and weight of pycnometer with solution respectively.

If the concentration is expressed in molarity (C), the equation (1.2.7) takes the form [30]:

$$\varphi_v = \left[\frac{M_2}{\rho_0} - \frac{1000(\rho - \rho_0)}{C\rho_0}\right] \cdots\cdots\cdots\cdots\cdots\cdots (1.2.9)$$

Where, the relation,

$C = \frac{m.\varphi_v.1000}{1000 + \varphi_v.m.\rho_0}$ is used for inter conversion of the concentration in the two scales [30]. The partial molar property of a solute is defined as the change in property when one mole of the solute is added to an infinite amount of solvent, at constant temperature and pressure, so that the concentration of the solution remains virtually unaltered. If ‘Y’ represents partial molar property of a binary solution at constant temperature and pressure, Y will then be a function of two independent variables n_1 and n_2, which represent the number of moles of the two components present. The partial molar property of component one is then defined by the relation:

$$\bar{Y_1} = \left(\frac{\delta Y}{\delta n_1}\right)_{n_2,P,T} \cdots\cdots\cdots\cdots\cdots\cdots (1.2.10)$$

Similarly for component 2,

$$\bar{Y_2} = \left(\frac{\delta Y}{\delta n_2}\right)_{n_1,P,T} \cdots\cdots\cdots\cdots\cdots\cdots (1.2.11)$$

The partial molar property is designated by a bar above the letter representing the property and by a subscript, which indicates the components to which the value refers. The usefulness of the concept of partial molar property lies in the fact that it may be shown mathematically as,

$$Y_{(n_1,n_2)} = n_1\bar{Y_1} + n_2\bar{Y_2} \text{ at constant T and P} \cdots\cdots\cdots\cdots (1.2.12)$$

In respect of the volume of solution, equation 1.2.4 gives directly

$$V = n_1\bar{V_1} + n_2\bar{V_2} \text{ at constant T and P} \cdots\cdots\cdots\cdots (1.2.13)$$

At infinite dilution, (m or c →0), the partial molar volume and the apparent molar volume are identical. To obtain reliable φ_v values, it is necessary to measure the densityρ, with great precision because errors in ρ contribute, considerably to the uncertainties in φ_v.

The concentration dependence of the apparent molar volume of electrolytes have been described by the Masson equation [31],the Redlich-Mayer equation [33]and Owen-Brinkley equation [32].Masson [31]found that the apparent molar volume of the electrolytes vary with the square root of the molar concentration as,

$$\varphi_v = \varphi_v^0 + S_v\sqrt{c} \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots (1.2.14)$$

Where, S_v is the experimental slope depending on the nature of the electrolyte.

Redlich and Rosenfeld [33] predicated that a constant limiting law slope S_v, should be obtained for a given electrolyte charge type if the Debye-Huckel limiting law is obeyed. By differentiating the Debye-Huckel limiting law for activity coefficients with respect to pressure, the theoretical limiting law slope S_v, could be calculated using the equation,

$$S_v = KW^{3/2} \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots \quad (1.2.15)$$

Where, the terms K and W are given by

$$K = N^2e^3\left(\frac{8\pi}{100D^3RT}\right)^{1/2}\left\{\left(\frac{\delta \ln D}{\delta p}\right)-\left(\frac{\beta}{3}\right)\right\} \cdots\cdots\cdots\cdots\cdots\cdots \quad (1.2.16)$$

And, $W = 0.5\sum \gamma_i Z_i^2 \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots (1.2.17)$

where, β is the compressibility of the solvent, γ_i is the number of ions of the species i of valency Z_i formed by one molecule of the electrolyte and the other symbols have their usual significance [33].For dilute solutions the limiting law for the concentration dependence of the apparent molar volume of electrolytes is given by the equation,

$$\varphi_v = \varphi_v^0 + KW^{3/2}\sqrt{C} \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots \quad (1.2.18)$$

and for not too low concentrations, the concentration dependence can be represented as,

$$\varphi_v = \varphi_v^0 + S_v\sqrt{C} + b_v C \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots \quad (1.2.19)$$

Where, S_v is the theoretical limiting law slope and b_v an empirical constant.

1.2.5 Determination of Apparent Molar Expansivities

From the apparent molar volumes determined at different temperatures, it is possible to derive the apparent molar expansivities through the thermodynamic relation given by equation 1.2.20.

$$\varphi_E = \left(\frac{\delta\varphi_v}{\delta t}\right)_P \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1.2.20)$$

Where,φ_E is the apparent molar expansivity, *t* is the temperature, and *P* is the pressure. The slope of φ_v versus *t* plot gave φ_E. The linearity of the φ_v versus *t* plot over a certain temperature range indicates that φ_E is constant over that range and given by the slope of the line. The apparent molar expansivity at infinite dilution, φ_{E}^{o}, can be obtained if φ_v^0 values are used for φ_v in this treatment.

1.2.6 Viscosity

Viscosity means viscous ability. The internal friction opposes the relative motion of adjacent layers of a fluid. When a fluid is flowing through a cylindrical tube, layers just touching the sides of the tubes are stationary and velocities of the adjacent layers increases towards the center of the tube, the layer in the center of the tube having the maximum velocity. There thus exists a velocity gradient. Molecules are a slower moving layer try to decrease the velocity of the molecules in a faster moving layer and vice versa, with a result that some tangential force is required to maintain uniform flow. This tangential force will depend upon two factors,

(i) Area of contact 'A' between the two layers and

(ii) Velocity gradient $\frac{dv}{dx}$

Thus, $f \propto A\frac{dv}{dx}$

Or $$f = \eta A\frac{dv}{dx} \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots \quad (1.2.21)$$

Where, η is a proportionality constant, known as the coefficient of viscosity or simply viscosity of the liquid. Thus, the coefficient of viscosity may be defined as the force per unit area required to maintain unit difference in velocity between two parallel layers of liquid unit distance apart.

The reciprocal of viscosity called the fluidity (ϕ) is given by the relation.

$$\phi = \frac{1}{\eta} \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots \quad (1.2.22)$$

If a liquid with a coefficient of viscosity (η) flows with a uniform velocity, at a rate of V cm^3 in t seconds through a narrow tube of radius r cm, and length 1 cm under a driving pressure of p dynes cm^{-2} then according to J.L.M. Poiseuille [34]:

$$\eta = \frac{\pi \mathrm{Pr}^4 t}{8lv} \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots \quad (1.2.23)$$

This equation known as Poiseuille's holds accurately for stream-line flow but not for the turbulent flow which sets as higher velocities. After correction for kinetic energy, the equation becomes,

$$\eta = \frac{\pi \mathrm{Pr}^4 t}{8lv} - \frac{\rho V}{8\pi lt} \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots (1.2.24)$$

Where, ρ represents the density of the liquid/solution. However, in practical purposes, the correction factor is generally ignored.

The driving pressure P=$h\rho g$, where h is the difference in height of the surface of the two reservoirs, since the external pressure is the same at the surface of both reservoirs, g = acceleration due to gravity andρ= the density of liquid. Thus the equation (1.2.23) becomes,

$$\eta = \frac{\pi h\rho g r^4 t}{8vl} \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots \quad (1.2.25)$$

For a particular viscometer *h*, *l*, *r* and *v* are fixed, so the equation (1.2.25) becomes,

$$\eta = A\rho t \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots \quad (1.2.26)$$

Where $A = \frac{\pi hgr^4}{8vl}$, called the calibration constant of the viscometer used.

Putting the values of A, ρ and to f the investigated liquid in equation (1.2.26), the coefficient of viscosity can be obtained for a liquid at a definite temperature.

The CGS Unit of viscosity is poise, in honor of J. L. M. Poiseuille. The SI unit of viscosity is the pascal-second (Pa·S). Since viscosity of liquid is usually very small, it is usually expressed in centipoise (cP) or mPa.S.

1.2.7 Viscosity and temperature

The viscosity of a liquid generally decreases with the increase of temperature. Evaluation of energy of activation for viscous flow can be stated by the Arrhenius equation as follows:

$$\eta = Ae^{-\epsilon_a/RT} \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots \text{(1.2.27)}$$

Where, A is Arrhenius constant and ε is energy of activation for viscous flow. The linear form of the equation 1.2.27 is as follows:

$$ln\eta = lnA - \frac{\epsilon_a}{RT} \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots \text{(1.2.28)}$$

$ln\eta$ vs $\frac{1}{T}$ offer straight line. From the slope and intercept the energy of activation and Arrhenius constant can be determined.

1.2.9 Different thermodynamic parameters

Eyring and co-workers [35] using absolute reaction rate theory and partition functions corrected viscosity, η as follows:

$$\eta = \frac{hN}{V}.e^{\frac{\Delta G^*}{RT}} \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots \text{(1.2.30)}$$

Where, ΔG^* is the change of free energy of activation per mole for viscous flow, $\boldsymbol{V_m}$ is the molar volume for liquids or solutions and h, N, R and T have usual meaning. The values of change of free energy of activation (ΔG^*) can be calculated by using the Nightingle and Benck equation [36],

$$\Delta G^* = \text{RT}\ln\left(\frac{\eta V}{hN}\right) \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \text{(1.2.31)}$$

And values for the corresponding thermodynamic parameters, enthalpy of activation, ΔH^* and entropy of activation ΔS^* for per mole for viscous flow of the liquids or solutions have been calculated from the relationship (1.2.30) [36]

$$ln\frac{\eta V}{hN} = \frac{\Delta H^*}{RT} - \frac{\Delta S^*}{R} \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots \text{(1.2.32)}$$

Assuming $\Delta \boldsymbol{H}^{*}$and $\Delta \boldsymbol{S}^{*}$to be almost independent in the temperature range studied, a plot of $\mathbf{ln}\,\frac{\boldsymbol{\eta V_m}}{\boldsymbol{Nh}}$ against$\frac{\mathbf{1}}{\boldsymbol{T}}$, will give a straight line. From the slope and intercept $\Delta\mathbf{H}^{*}$and $\Delta \boldsymbol{S}^{*}$ can be determined respectively.

Chapter II

Literature review

2.1 Literature review

N-acetylcysteine (NAC) a sulfhydryl substance is a derivative of amino acid L-cysteine widely used as medicine. Mucolytic activity of NAC was used for the first time in the treatment of some respiratory diseases (e.g. chronic bronchitis) over 40 years ago [46]. Detoxifying properties of NAC were discovered in the 1970s and since then NAC was being used as an antidote in aminophen intoxication [47]. Currently it is known mainly as an antioxidant displaying direct and indirect activities [48]. Oxidative stress – the imbalance between reactive oxygen species (ROS) and actions of the antioxidant network – takes part in pathogenesis of a broad spectrum of diseases including cancer, cardiovascular, arthritis, diabetes, influenza-like symptomatology as well as some lung disturbances namely pulmonary oxygen toxicity, adult respiratory distress syndrome, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis [49] and cystic fibrosis. Increasing number of publications confirm efficacy of using NAC in the above mention diseases [48-51]. Antioxidant properties of NAC come from its specific structure. N-acetylcysteine contains amino acid L-cysteine plus an acetyl (-$OCCH_3$) group attached to the amino (NH_2) group. All amino acids including L-cysteine with sulphur group are characterized by antioxidant properties. Since L-cysteine is a precursor of reduced glutathione (GSH), synthesis of NAC contributes to augmentation of the level of this major intracellular antioxidant [48]. Depleted pool of GSH is often caused by oxidative stress and inflammation. N-acetylcysteine can therefore normalize disturbed redox status of the cells and thus influence redox – sensitive cell signaling and transcription pathways. Sulfhydryl group (–SH) in the NAC molecule make possible also to directly scavenge ROS such as superoxide radical (O_2), hydrogen peroxide, regulation of protein phosphorylation and regulation of calcium level inside the cells as well as phagocytosis process[52, 53].

Diversity of applying NAC is the source of broad spectrum of used dosage and routes of administrations. Oral administration (tablet or inhalations) can range from 250 to 1800 mg/day and is used mainly in lung diseases [49]. Toxicological data shows that intakes of NAC per day orally could be consumed without causing significant adverse effects [54]. Application of NAC (7 mg/ml) diminished UV induced ROS in melanocyte cell line and protects these cells from UV – induced oxidative damage. N-acetylcysteine reduced formation of 8-oxoguanine in mice skin protecting melanocytes from UV induced melanoma [55-57]. Most of anticancer therapies are based on growth of ROS production in cancer cells leading to their apoptosis [58-62]. The efficiency of vitamin E and NAC as an antioxidant adjuvant therapy was shown in chemotherapy/radiotherapy course during acute lymphoblastic leukemia in 40 children study. Toxicity of chemo- and radiotherapy measured as a diminished level of malondialdehyde, as well as increased level of glutathione peroxidase and decreased occurrence of toxic hepatitis was significantly reduced [63-65].

N-acetylcysteine as a mucoactive, anti-inflammatory and antioxidant agent was expected to have a benefit therapeutic effect in Cystic fibrosis patients. In 4 weeks trial [66-68] NAC was administered orally to 18 Cystic fibrosis patients in a high doses (600-1000 mg) three times daily. Endometriosis is known as a common gynaecological disorder affecting about 10% of women in a reproductive age. It is characterized by presence of endometrial tissue outside of the uterine cavity, resulting in pelvic pain, infertility and dysmenorhea. Development of the disease is caused by implantation of endometrial cells in the peritoneal cavity and their proliferation leading to invade peritoneum and disease progression. Pathophysiology of endometriosis includes chronic inflammation within oxidative stress and pathological angiogenesis [69-70].

A cataract is a cloudiness or opacity in the normally transparent crystalline lens of the eye. This cloudiness can cause a decrease in vision acuity and sometimes may lead to hand movements behind the eye or blindness. The leading risk factor of cataract is aging.

As glutathione is an important antioxidant in the lens it has been suggested that increasing GSH level NAC supplementation could be used to reduce cataract risk [71].

Diabetes elevates the risk of cataract formation. This form of cataract can result from sorbitol accumulation in the lens. Pathophysiology of early cataract development and the potential benefit of supplementation with vitamin B6 and NAC among the diabetic population were studied by Jain *et al.* [72]. High-glucose concentrations can cause the oxidation and modification of proteins in the lens. Vitamin B6 (pyridoxine) and NAC supplementation may be helpful in slowing the oxidation of lens proteins. The study of Liebermann [73] raised the possibility that administration of NAC may reverse early cataracts. Zhang et al. [74] evaluated the effect of NAC and glutathione ethyl ester (GSH-EE) eye drops on the progression of diabetic cataract formation in rats. Author concluded that NAC and GSH-EE can slightly inhibit the progression of the diabetic cataract at the earlier stage. N-acetylcysteine, used as an ophthalmic drug is promising in the treatment of a range of ophthalmic disorders with oxidative stress component involved in pathogenesis including cataract, glaucoma, dry eye syndrome, vitreous floaters, inflammatory disorders, corneal, retinal and systemic diseases and its ophthalmic complications.

Water is universal solvent used in daily life. Ethanol is the organic solvent also extensively used in various sectors. So investigation of interaction between NAC and water, NAC and ethanol or NAC and ethanol-water mixture could be quite interesting and applicable as well that has not been investigated earlier so far.

2.2 Aim of the research

N-Acetyl-l-cysteine (NAC) is a molecule of extremely fast medicinal career and wide therapeutic profile. To date, at least 12 distinct biological activities have been attributed to NAC. In view of the fact that NAC is one of the smallest drug molecules, with a total of 19 atoms, the above pharmacological versatility is undoubtedly unique, indicating that the background of its biological complexity must be sought at the sub-molecular level. NAC is an acetylated amino acid with antioxidant and mucolytic properties. These two activities have made NAC particularly relevant in cystic fibrosis studies, where the antioxidant/reducing character of the compound is described to ameliorate the characteristic systemic redox imbalance state of cystic fibrosis and the mucolytic properties of the compound are shown to impede upon the congestion and inflammation correlated to this redox state. NAC shows complimentary action to glutathione, both demonstrating antioxidant activity through their thiol functionality, and both are shown to protect against peroxidative stress related to septic shock. NAC has also been shown to induce apoptosis in vascular smooth muscle cells, indicating that these cells respond differently to changes in reduction-oxidation state than other tissues that are normally protected by the presence of antioxidants. This observation in vascular smooth muscle cells indicates NAC as an interventional tool upon arteriosclerotic proliferation of these cells. NAC is the most widely used mucolytic agent worldwide. Further indications for its use include rheumatoid arthritis, plasma hyperlipoproteinaemia and adult respiratory distress syndrome. NAC has also been reported to support repair processes after cytotoxic and radioactive damages in cancer therapy to remove atherosclerotic plaques. Its mode of action has generally been assumed to be related to the thiol (or thiolate) site, as the key moiety of the molecule. The reported thiolate-involved mechanisms are free radical scavenging, rupture of disulfide bonds in cross-linked mucous proteins, metal complex formation. Some papers claim that NAC penetrates the cell membranes. Some others deny that, on the basis of its poor (5%) bioavailability and very low alveolar concentration after oral administration. The chemical properties of NAC have been characterized in terms of metal complexation constants, analytical stability in various pharmaceutical products, and protonation constants, determined by UV−pH titration and kinetic methods. NAC contain thiol and adjacent carboxylic acid group. The quantitation of thiol−disulfide oxidation−reduction potentials is a difficult task and can be achieved for limited kinds of compounds only. The formation of stable metal−thiolate complexes at electrode surfaces and the concomitant electrochemical irreversibility prevent the use of standard voltammetric methods .Reaction mixture analysis of thiol−disulfide equilibrium systems were done by spectroscopic techniques .The recently observed relationship between the basicity and oxidizability of thiolates is a significant progress in the biological chemistry of these compounds, providing a means to characterize the thiol−disulfide chemistry, even for compounds with more than one thiolate site.

It is obvious that NAC has some crucial properties that govern its viability and activity in biological media. So its solution behavior and the related protonation state and medium-dependent physicochemical interaction and thermodynamic properties are the discussion point at this time. To the best of our knowledge, still there is no explicit data of rheological and volumetric properties of N-acetylcysteine in Ethanolic and aqueous system are available. The purpose of this study was to evaluate the miscibility of N-acetylcysteine in water, ethanol and aqueous-ethanolic mixed solution systems. Physico-chemical study recognized useful tool in getting sound information about the structure of various solution system. The specific aims of this study are:

i) to be aware of the probable interaction between water + n-Acetyl-L-cysteine solution, ethanol + n-acetylcysteine solution, water + ethanol+ n-acetylcysteine ternary solution.

ii) to explore the data on physico-chemical properties of the systems mentioned in i).

iii) to explore the role of n-acetylcysteine in physico-chemical interactions of the systems mentioned in i).

iv) to understand the change of thermodynamic properties of n-acetylcysteine in water, ethanol and/or water-ethanol mixture.

CHAPTER III

Experimental

3.1 General

During the course of the present work a number of techniques were involved which were in general standard ones. Constant efforts for attaining the ideal conditions for the experiments were always attempted.

The thoroughly cleaned glass pieces were dried in electric oven. The smaller pieces of apparatus were dried in electric oven and stored in desiccators, while larger pieces of apparatus were used directly from the oven.

Ostwald viscometers were used for measurement of viscosity. The inside wall of the viscometer was cleaned thoroughly with warm chromic acid so that there was no obstruction in the capillary and the liquid could run clearly without leaving any drop behind. It was then rinsed thoroughly with distilled water followed by rectified spirit and finally with acetone and dried.

3.2 Apparatus

The glass-ware used for the measurement for density of solvents and solutions were of the specific gravity bottle (pycnometer). Viscosities of various liquids were measured using Ostwald type viscometer, A & D Company. Electronic balance (HR 200, made in Japan) with an accuracy of± 0.0001g was used for weighing. The flow time of liquids were recorded by a stop-watch capable to read up to 0.01 seconds. The temperature was controlled by water thermostat (Fisher Scientific ET-150, HAKKE, Germany) with an accuracy of ± 0.05°C. The experimental temperatures were 298.15 to 323.15K at 5K intervals. Both the density bottle and viscometer were calibrated with doubled-distilled water at the studied temperature. Calibrated volumetric flask, pipette and burette were used for necessary volume measurement.

3.3 Preparation and Purification of Reagents

High quality analytical grade reagents were used in all the experiments, where necessary further purifications were done.

3.4 Distillation of water

First time water was distilled by water distillation apparatus. First time distilled Water was further purified by a quick-fit glass made distillation apparatus. About 1.5 L water was taken in a round bottom reservoir of which the capacity was 2.0 L. Then it was distilled in presence of $KMnO_4$. Distilled water was collected at only 100°C. Other liquids of which the temperatures were below and above the mentioned boiling point were discarded. In all the experiments double distilled water was used.

3.5 Chemicals

N-acetylcysteine was collected from Sigma Aldrich, USA. High performance liquid chromatography (HPLC) grade Ethanol was collected from E-Merk, Germany, and was 99.99% pure. All chemicals and reagents were of analytical grade and were used without further purification.

3.6 Preparation of solution

Solutions were prepared by mixing appropriate volumes of components. The volume taken by using burettes and pipettes were correct up to 0.1 cm^3. The volume of each component used as taken converted into mole fraction, special precaution was taken to prevent evaporation and introduction of moisture into the experimental samples.

3.7 Density measurement

The densities of the solutions were determined by weighing a definite volume of the solution in a calibrated pycnometer (Glassgo, India) at specified temperature. The volumes were obtained by measuring the weight of water at that temperature and using the density of water from literature. The density of solution was determined from the relation.

$$\rho = \frac{w - w_e}{v_0} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.1)$$

Where, ρ = density of the solution, w = weight of bottle with solution, w_e = weight of empty bottle, v_0= volume of bottle.

The density bottle was first thoroughly cleaned with warm chromic acid and then with enough distilled water. Then it was rinsed with acetone and finally dried at $85^{O}C$ for more than two hours. The weight of the dried empty density bottle was noted after proper cooling. The density bottle was further calibrated at experimental temperature with doubly distilled water.

The solution under investigation was taken in a density bottle up to the mark. The density bottle was clamped carefully with stand in the thermostatic water bath maintained at the desired temperature. As the solution started to gain the temperature of the bath excess liquid overflowed through the capillary. Then it was allowed to keep in the bath for about 30 minutes to attain the thermal equilibrium. When no overflowed observed through the capillary the density bottle was taken out from the thermostatic water bath, wiped with tissue-paper, dried and weighed carefully in the analytical balance. The difference between the two weights (weight with solution and without solution) gave the weight of the solution in the density bottle. The density measurement was performed for each of the solutions at the temperature 298.15, 303.15, 308.15, 313.15, 318.15 and 323.15K respectively in this way using equation (3.1).

3.8 Viscosity measurements

Viscosity of water, ethanol and several solutions were measured by using the Ostwald U-type viscometer. The interior of the viscometer was cleaned thoroughly with warm chromic acid and then with distilled water, so that there was no obstruction in the capillary and the liquid could run freely without leaving any drop behind. It was then rinsed with acetone and dried in and oven at about 85°C. The viscometer was then clamped vertically in the thermostatic water bath such that the upper mark of the top bulb was well below the water level. 10.0 mL of doubled-distilled water was poured into the viscometer by a pipette.

Then it was allowed to keep in the thermostatic bath for about 30 minutes to attain the bath temperature. With the help of pipette filler attached to the narrower limb of the viscometer, the water was sucked up above the upper mark of the bulb. The water of bulb was then allowed to fall into the capillary and the time of fall between the two marks was noted with the help of stop-watch capable of reading up to 0.01 second. The reading at each temperature was repeated three or four times, in order to check the reproducibility of the flow time, the temperature being maintained at the same value. Since the accurate viscosity and density of water at different temperatures are known (from literature) calibration constant A of the viscometer for different temperature were obtained by using equation,

$$\eta = A\rho t \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots (1.2.26)$$

Where, $A = \frac{\eta_{H_2O}}{\rho_{H_2O}.t_{H_2O}}$

Like water the flow time of different solutions were determined. Then putting the values of the calibration constant, density and time of flow of the experimental solutions, the viscosities of the solutions were determined by using the equation 1.2.26.

3.9 Apparent Molar Volumes measurement:

Apparent molar volumes were determined from measured densities of solvent and solution by using the following equation 1.2.8.

$$\boldsymbol{\varphi_v} = \left[\frac{1000(\rho_0 - \rho)}{C\rho_0}\right] + \frac{M_2}{\rho_0} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1.2.8)$$

Where $\varphi_v$is the apparent molar volume, C is the molarity, M_2 is the molecular mass of the solute (NAC), and ρ_0 and ρ are the densities of the solvent and the solution respectively. In general, $\varphi_v$was found to vary linearly with concentration for the systems studied. Thus, $\varphi_v$data were fitted into equation1.2.14 and 1.2.19.

$$\varphi_v = \varphi_v^0 + S_v\sqrt{c} \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots (1.2.14)$$

$$\varphi_v = \varphi_v^0 + S_v\sqrt{C} + b_vC \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots (1.2.19)$$

Where $\boldsymbol{\varphi_v}$ is the apparent molar volume at infinite dilution and $\boldsymbol{b_v}$ is an experimentally determined parameter.

3.10 Determination of Apparent Molar Expansivities

From the apparent molar volumes determined at different temperatures, it is possible to derive the apparent molar expansivities through the thermodynamic relation given by equation 1.2.20.

$$\varphi_E = \left(\frac{\delta\varphi_v}{\delta t}\right)_P \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (1.2.20)$$

Where φ_E is the apparent molar expansivity, *t* is the temperature, and *P* is the pressure. The slope of φ_v versus *t* plot gaveφ_E. The linearity of the $\varphi_v$versus *t* plot over a certain temperature range indicates that φ_E is constant over that range and given by the slope of the line. The apparent molar expansivity at infinite dilution, φ_{E}^0, can be obtained if φ_v^0 values are used for $\varphi_v$in this treatment.

3.11 Determination of Thermodynamic Parameters

The activation energy for viscous flow is determined from logarithmic form of Eyring equation as:

$$ln\eta = lnA - \frac{\epsilon_a}{RT} \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots (1.2.28)$$

The slope and intercept of the straight line of plot of $ln\eta$ vs $\frac{1}{T}$ presented the values of activation energy for viscous flow and Arrhenius constant respectively.

Values of enthalpy of activation, ΔH^* and entropy of activation, ΔS^* for per mole for viscous flow of solutions have been calculated from the relationship (1.2.30)

$$ln\frac{\eta V}{hN} = \frac{\Delta H^*}{RT} - \frac{\Delta S^*}{R} \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots (1.2.30)$$

CHAPTER-IV

Results and Discussion

4.1 General

The interaction of NAC in water, ethanol and aqueous alcoholic solution were investigated. The experimental outcomes and the properties were derived from the experimental data are presented in this section. The effort of this chapter include:

- Study of interaction between NAC and ethanol
- Study of interaction between NAC and water
- Study of interaction NAC in (ethanol–water)
- Compute and investigate the volumetric and viscometric properties of the investigated system.
- Compute and analyze various thermodynamic parameters such as, free energy, enthalpy and entropy of the experimented systems.

From these studies various information about binary and ternary mixtures of NAC were obtained, which are presented in various sections and discussed in the light of theories stated earlier. NAC is a derivative of cysteine with an acetyl group attached to its nitrogen atom and like most thiol can be oxidized and also served as a nucleophile which chemical structure has –COOH, – SH, CH_3CONH– groups. The characteristic chemical behavior of NAC is determined by their functional groups –COOH, –SH, CH_3CONH–. NAC can donate protons easily as the conjugated base is resonance stabilized.

Following forces may play between NAC when it is in protic and aprotic solvent.

1. **Van der Waals forces**: the natural stickiness of each individual atom, caused by the movement of its electron cloud. While small, this effect can be substantial when two molecules can line up close to one another.
2. **Electrostatic charge**: the ions of a side chain that have either plus or minus charges. In a charged side chain, an atom either losses electron and becomes a positive ion or gains electron and turns into a negative ion.
3. **S···S interaction:** Several sulfur (S)-containing substance, such as NAC, interact with each other, that link two different molecules together. They often form loops in the otherwise straight chains. Every S···S interaction between two molecules of NAC may serves as a "staple" and hold them together.

4. **H-bond:** H-bond may play a significant role when NAC is dissolved in water and ethanol.

But detail process what happens when NAC is dissolved in ethanol and water in its binary and ternary mixtures may be drawn from volumetric and viscometric properties has been discussed in the following sections.

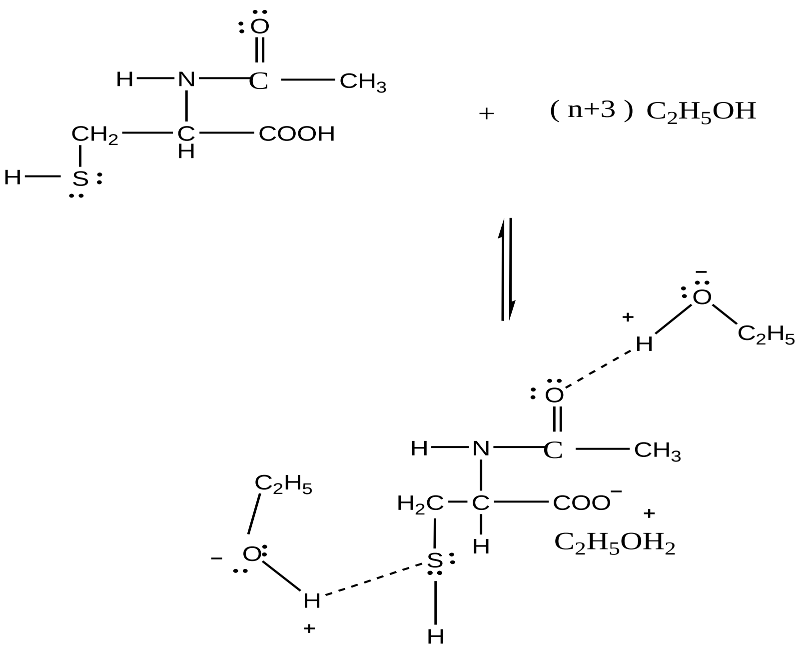
4.2 Volumetric Properties

4.2.1 Density

Ethanol–NAC system

The density values, ρ of the ethanol and [ethanol–1% (w/v)NAC], (ethanol–5%(w/v) NAC), (ethanol–10%(w/v)NAC), (ethanol–15%(w/v)NAC) and (ethanol–18%(w/v) NAC) systems have been investigated at 298.15, 303.15, 308.15, 313.15 and 318.15 K. The density values of binary systems have been shown in Table 4.2 at different temperatures, while the experimented densities of pure ethanol at mentioned temperatures have been shown in Table 4.1 together with the literature values, for possible comparison. The agreement between the measured and literature values have been found to be reasonable. Composition of NAC in ethanol were varied from 1 to 18 (w/v)% at 5 K intervals from 298.15 K to 318.15 K as mentioned in the Table 4.2. From the results shown in Table 4.1 and 4.2 it can be stated that densities of ethanolic solution of NAC are higher than those of the pure ethanol. It is also seen that the densities of NAC solutions in ethanol increased remarkably with concentration at all the temperatures but decreased with increasing temperature at a constant concentration. Results of the Table 4.2 has been fitted in Figure 4.1. From the Figure 4.1 it is seen that density values of NAC in ethanol increased almost linearly with the concentration of the NAC within the temperature range of 298.15 K to 318.15 K at 5 K intervals. This is may be due to the increase in density in NAC–ethanol binary system may be due to solute–solvent interaction through strong hydrogen bond, dipole-dipole as well as acid–base interaction between NAC and ethanol. The polarity and dipole moment of ethanol is 0.654 and 1.69D [42]. When NAC is dissolved in ethanol, the probable solvation is presented below:

Carboxylic acid functional group of NAC molecules release proton and the conjugate base is stabilized by $C_2H_5OH_2^+$.The amide group of the NAC forms dipole-dipole interaction with the ethanol. The structure forms H–bond with ethanol. The amide and thiol groups of NAC forms dipole-dipole interaction with ethanol.



Solvation of ethanol and NAC molecules

Water–NAC system

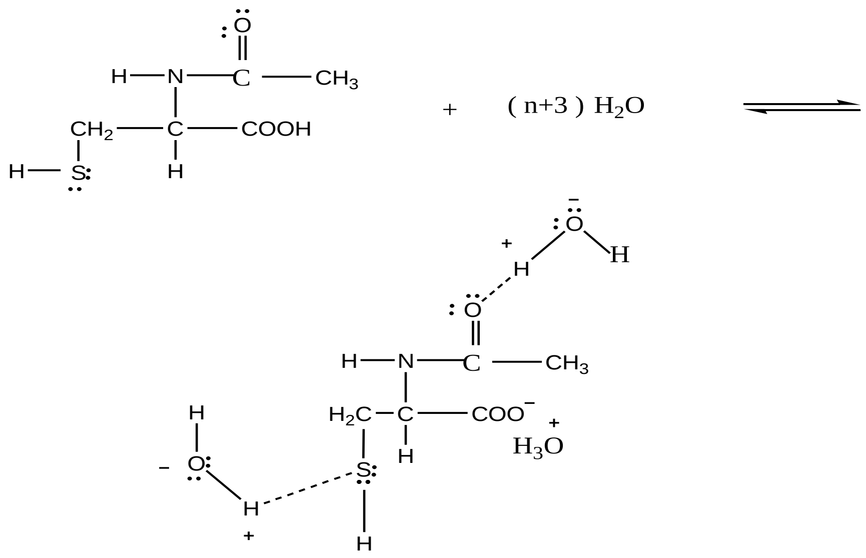
The density values, ρ of the water and (water –1%(w/v)NAC), (water–5%(w/v)NAC), (water–10%(w/v)NAC), (water–15%(w/v)NAC), (water–18%(w/v)NAC), systems at 298.15, 303.15, 308.15, 313.15 and 318.15 K have been investigated. The density values are shown in Table 4.2. The density values of (water–NAC) systems at 5 investigated temperatures are higher than those of water even the values increased with increasing the amount of NAC in water. It is seen from the result that densities of aqueous NAC solution increased with increasing concentration with in the investigated composition, 1-18%(w/v) of NAC in water. Comparing the results in Table 4.2 with the literature value of water, it can be stated that density values of solution of NAC in water are higher than the density values of water. Density results of the water–NAC Table 4.2 were fitted in Figure 4.2. From the Figure 4.2 it is seen that density values of NAC in water increased almost linearly with the concentration of the NAC within the temperature range of 298.15 K to 318.15 K at 5 K intervals but decreased with increasing temperature at a constant concentration. This is may be due to the increase in density in water–NAC binary system may be due to solute-solvent interaction through strong hydrogen bond, dipole-dipole as well as acid-base interaction between NAC and water. Detail mechanism of dissolution of NAC in water is still unknown. But we know that water is a polar inorganic molecule which have dipole moment 1.84D. Due to the high dipole moment and the charge separation of –O–H bond, water molecules form hydrogen bonds with each other and recent studies confirm that the room temperature liquid water comprises of large fraction of broken H–bond and each molecule only forms two strong H–bonds: one acceptor and one donor and this implies that liquid water comprises of primarily rings or chains. This high polarity and the extent of H–bond is responsible for the unique characteristics of water and dissolving of polar substances like acids and alcohols by establishing H–bonds. It is also an idle amphoteric substance and on self-ionizing it produces H_3O^+ and OH^-. The dissociation constant for this dissociation is commonly symbolized as Kw and has a value of about 10−14 at 25 °C. Three type's interactions can be occurred when NAC is dissolved in aqueous solution, which are described below:

When NAC is dissolved in water, water-NAC system experienced acid-base, dipole-dipole interaction and H–bond formation results of strong intermolecular attraction. For this, the total volume of water-NAC solution is decreased than solvent, pure water. So the density of water-NAC is higher than water as in Table 4.1 and 4.2.

NAC molecules in aqueous solution behave as weak acid because of its –COOH functional group that release proton and exhibits negative charge and H_3O^+ available in water come near about it for balance.

$$\underset{\text{NAC}}{C_5H_9NO_3S} + H_2O \rightleftharpoons \underset{[\text{NAC}]^-}{C_5H_8NO_3S^-} + H_3O^+$$

The amide group of NAC forms H–bond with water. Thiol group of the NAC forms dipole-dipole interaction as well as H–bond with water. The solvation system can be shown as follows:



Solvation of NAC and water molecules

Ethanol–water–NAC system

The densities, ρ of the [4:1] ethanol–water–NAC, [3:2] ethanol–water–NAC, [2:3] ethanol–water–NAC, [4:1] ethanol–water–NAC, [1:4]ethanol–water–NAC, systems at 298.15K to 318.15 K at 5K interval has been investigated. The density values are shown in Table 4.4. The density values of ethanol–water–NAC, ternary systems are higher than those of NAC–water and NAC–ethanol the binary systems. The density values increased with increasing concentration of the NAC in ethanol–water at the entire investigated composition range, 1-18 (w/v) % NAC in mixed solvents. Comparing the results in Table 4.1, 4.2, 4.3 and 4.4, it can be stated that densities of NAC in ethanol–water increased remarkably with concentration at all the temperatures. Results of the table 4.4 are fitted in figure 4.3-4.6. From the figures it is seen that the densities of NAC in [4:1], [3:2], [2:3], [1:4] ethanol–water systems increased almost linearly with the concentration of the NAC within the temperature range of 298.15 K to 318.15 K at 5 K intervals.

The increase of density values of NAC with concentrations can be attributed to the increase in solvent-solvent, solute-solvent and the solute-solute interactions. In the case of solvent-solvent (ethanol–ethanol, water–water, ethanol–water) interaction and solute–solvent (NAC–ethanol, NAC–water) already discussed earlier. Not only ethanol serves as a protic solvent but also aprotic solvent because of moderate dipole moment and long hydrocarbon residues. When ethanol dissolved in water, with increase of the ratio of ethanol in water, the aprotic nature of characteristics increased. NAC when it is in aprotic solvent may interact with another NAC molecule through an additional interaction can be termed as solute–solute interaction, making S···S linkage that link two molecules together. Every S···S linkage made between two molecules of NAC serves as a "staple" holding them in a more steady position. This S···S linkage is so weak and breaks when heated, even at moderated temperature. At the same time it is seen that the densities decrease significantly with increasing temperature at a constant concentration as in shown Table 4.4 and Figure 4.3-4.6. The density value vs $\frac{1}{T}$ of NAC have plotted Figure 4.7-4.12. With the increase of temperature the internal energies of the systems are increased and the solute–solvent, solvent–solvent and solute-solute interaction might be weakened. The consequence is the decrease in density values. All the binary and ternary systems, with the increase of concentration densities are raised due the dipole-dipole, acid-base and hydrogen bond interaction between the NAC–ethanol and NAC–water, NAC–ethanol–water and the stearic hindrances of NAC molecules. The density of binary system are presented below.

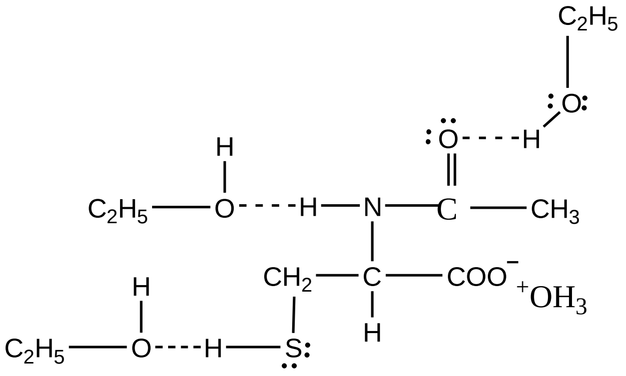
Water–NAC > ethanol–NAC

In case of ternary systems, the highest densities are observed [1:4] ethanol–water– NAC system, probably highest dipole moment as well as interaction are strongly occur here. On the contrary [4:1] ethanol–water–NAC system, probably lowest dipole moment as well as interaction are occur here, comparison in ternary systems. Ternary systems, the intensity of the interaction are increased with the increase of the ratio of water.

[4:1] ethanol–water–NAC < [3:2] ethanol–water–NAC < [2:3] ethanol–water–NAC < [1:4] ethanol–water–NAC

Detail mechanism of dissolution or solvation of NAC in ethanol–water system is still unknown. Here a possible mechanism has been proposed. We know that hydrophilic NAC molecules are attracted by water molecules. Unlike the charged side chains, polar side chains are overall neutral, but still capable of attracting water to places on their surface. They neither gain nor lose an electron but simply shift the electron towards one of the atoms. Such a polar side chain remains neutral as a whole, but the separation of the "pluses" and "minuses" within it creates two opposite "poles", each capable of attracting water molecules.

Water is little bit denser than ethanol. At 298.15K temperature and standard pressure, the ethanol have densities of about 0.7858 g/cc compare to water at the same conditions with a density of 0.997 g/cc. As to the reason, water is denser than alcohol largely because of the arrangement of its molecules. The molecules of water are closely packed than that of ethanol [41].



Solvation of ethanol,water and NAC molecules

In case of ethanol–NAC system dipole–dipole interaction is lower comparisons with water–NAC system because of the polarity and dipole moment of water is 1 and 1.84D [43], whereas polarity and dipole moment of ethanol is 0.654 and 1.69D. Hydrogen bond formation is higher of water–NAC than ethanol–NAC system because of the dipole moment and polarity of water is more than ethanol solvent. With the increase of dipole-dipole interaction and H–bond formation, results in stronger intermolecular attractions as well as volume of solution are decreased as density is increased. The data of Table 4.2 are support on this assumption. Ethanol–water mixtures are very important systems exhibiting properties that are of great interest in physics, chemistry and biology. These include several thermodynamic and physico-chemical properties. For instance, the mixture of alcohol and water exhibits an entropy value that is smaller than expected which leads to the concept of negative excess entropy [42]. Most of these intriguing aspects are consequence of the great ability of both water and alcohol to make hydrogen bonds. The negative entropy of ethanol-water mixtures arises due to the interplay between the relative strengths of the ethanol-ethanol, ethanol–water water–water and hydrogen bonds. Ethanol–water systems can have two hydrogen-bonded structures corresponding to the two possible heterodimers where ethanol is a proton acceptor, $CH_3CH_2HO….H_2O$, or a proton donor, $CH_3CH_2OH……OH_2$. In the water-ethanol heterodimer the R_{O---O} and the R_{O----H} is 2.843 Å and 1.90 Å and the dipole moment is 1.944 D and in ethanol-water heterodimer the R_{O---O} and the R_{O----H} is 2.914 Å and 1.951 Å and the dipole moment is 2.494 D and the earlier one is the most stable heterodimer where water plays the role of proton donor [42]. Ethanol and water molecule form OH^- and $C_2H_5OH_2^+$ ions. Carboxylic group of NAC react with OH^- ion and produce water by loss a proton. Thiol group undergoes dipole-dipole interaction with ethanol. The oxygen of carbonyl group pulls the electron towards himself and hold negative charge. Lone pair electron of nitrogen atom fill up the electron deficiency of carbonyl carbon. The structure established H-bond with water.

Ternary systems presents are two polar molecules ethanol and water. Due to this polar mixture solvent dipole-dipole interaction are occur highest and density is highest. Ethanol–water mixture solvent dipole moment is 2.494D, Which is highest than water and pure ethanol solvent. Due to the largest dipole moment of ethanol-water mixture than water and pure ethanol solvent, total volume of ternary system will be reduced than binary system. As well as, the density of NAC–ethanol–water will be highest than NAC-ethanol and NAC–water system. The data of Table 4.2 and 4.4 support this explanation. And the highest density are observed [4:2] ethanol + water +NAC system, probably highest dipole moment as well as interaction are stronger. On the contrary [4:1] ethanol +water + NAC system, probably lowest dipole moment as well as interaction are occur here, comparison in ternary systems. Acid–base interaction carboxylate anion of NAC molecules tend to stick together with hydronium ion. During the experiment, it observed that when NAC mixed with solvent, ternary system is cooler than binary system. On the other hand, in the binary system water-NAC is cooler than ethanol-NAC. We know that, increasing the temperature of a substance (with a few exceptions) decreases its density by increasing its volume. So here, the density ternary system is higher than binary system. However, experimental data established of the endorsement in this connection.

The density maxima follow the order for binary and ternary systems:

[1:4] ethanol–water–NAC > [2:3] ethanol–water–NAC > [3:2] ethanol–water–NAC > [4:1] ethanol–water–NAC > water–NAC > ethanol–NAC

Table 4.1: Density values ($gm.cm^{-3}$), ρ and viscosity values (mPa.S), η of ethanol Literature and experimental values at 298.15 to 318.15 K at 5 K interval.

Temperature (K)	Density (gm.cm^{-3})		Viscosity (mPa.S)	
	Literature Value	Experimental Value	Literature Value	Experimental Value
298.15	0.7858[37]	0.7894	1.0820[38]	1.0889
303.15	0.7813[37]	0.7850	0.9870[38]	0.9895
308.15	0.7761[37]	0.7804	0.9015[39]	0.9073
313.15	0.7718[37]	0.7765	0.8284[40]	0.8332
318.15	0.7651[37]	0.7723	0.7642[39]	0.7718

Table 4.2: Density values (gm.cm^{-3}), ρ of N-Acetylcysteine in ethanol and water System at 298.15 to 318.15 K at 5 K interval

Name of the system	Conc./ (w/v)%	ρ (gm.cm^{-3})				
		298.15 K	303.15 K	308.15 K	313.15 K	318.15 K
Ethanol–NAC	1	0.795679	0.791223	0.786275	0.782309	0.77793
	5	0.812157	0.807897	0.803348	0.799538	0.79479
	10	0.834689	0.830497	0.825741	0.821664	0.81666
	15	0.856255	0.851954	0.847527	0.844017	0.83866
	18	0.863819	0.859613	0.855221	0.851331	0.84738
Water–NAC	1	0.999891	0.998472	0.996692	0.994758	0.99262
	5	1.010813	1.008872	1.006753	1.004951	1.00233
	10	1.023991	1.021964	1.019122	1.016588	1.01405
	15	1.037054	1.034290	1.031291	1.027720	1.02525
	18	1.043692	1.040818	1.038025	1.034368	1.03068

Table 4.3: Density values (gm.cm^{-3}), ρ of [4:1], [3:2], [2:3], [1:4] ethanol–water System at 298.15 to 318.15 K at 5 K interval

Name of the system	ρ (gm.cm^{-3})				
	298.15K	303.15K	308.15K	313.15K	318.15K
[4:1] ethanol+ water	0.81044	0.80623	0.80134	0.79834	0.79454
[3:2] ethanol+ water	0.84066	0.83585	0.83140	0.82779	0.82382
[2:3] ethanol+ water	0.87959	0.87561	0.87084	0.86726	0.86368
[1:4] ethanol+ water	0.93217	0.92816	0.92615	0.92334	0.918138

Table 4.4: Density values (gm.cm^{-3}), ρ of N-Acetylcysteine [4:1], [3:2], [2:3], [1:4] ethanol–water System at 298.15 to 318.15 K at 5 K interval

Name of the system	Conc. (w/v)%	ρ (gm.cm^{-3})				
		298.15 K	303.15 K	308.15 K	313.15 K	318.15 K
[4:1] ethanol– water –NAC	1	0.81673	0.81249	0.80745	0.80441	0.80057
	5	0.83311	0.82838	0.82313	0.81991	0.81589
	10	0.85527	0.84978	0.84484	0.84021	0.83602
	15	0.87599	0.87070	0.86569	0.86077	0.85573
	18	0.88820	0.88190	0.87649	0.87252	0.86738
[3:2] ethanol–water –NAC	1	0.84657	0.84164	0.83683	0.83299	0.82885
	5	0.86992	0.86398	0.85824	0.85252	0.84842
	10	0.89449	0.88868	0.88355	0.87696	0.87174
	15	0.91402	0.90864	0.90448	0.89986	0.89618
	18	0.92064	0.91628	0.91084	0.90665	0.90312
[2:3] ethanol–water –NAC	1	0.88655	0.88036	0.87487	0.87118	0.86756
	5	0.90365	0.89664	0.88993	0.88556	0.88195
	10	0.92172	0.91466	0.90856	0.90174	0.89727
	15	0.93723	0.93132	0.92619	0.91849	0.91406
	18	0.94345	0.93934	0.93291	0.92480	0.91918
[1:4] ethanol–water –NAC	1	0.93625	0.93212	0.92994	0.92695	0.92169
	5	0.95190	0.94763	0.94492	0.94075	0.93551
	10	0.97040	0.96454	0.96110	0.95734	0.95232
	15	0.98241	0.97667	0.97398	0.96995	0.96469
	18	0.98744	0.98322	0.98102	0.97795	0.97312

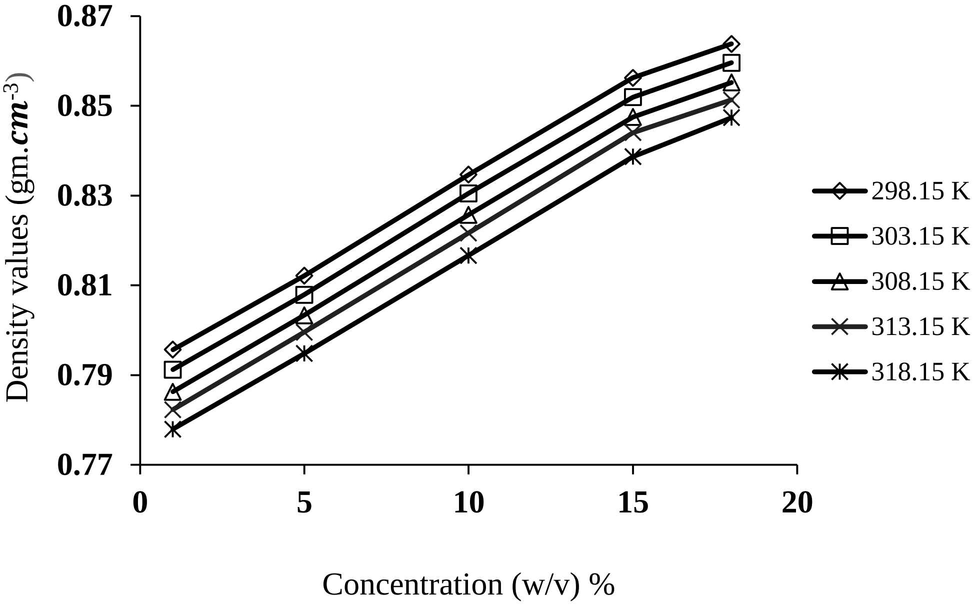


Figure 4.1: Densities, ρ of N-Acetylcysteine in ethanol at 298.15 to 318.15 K at 5 K interval

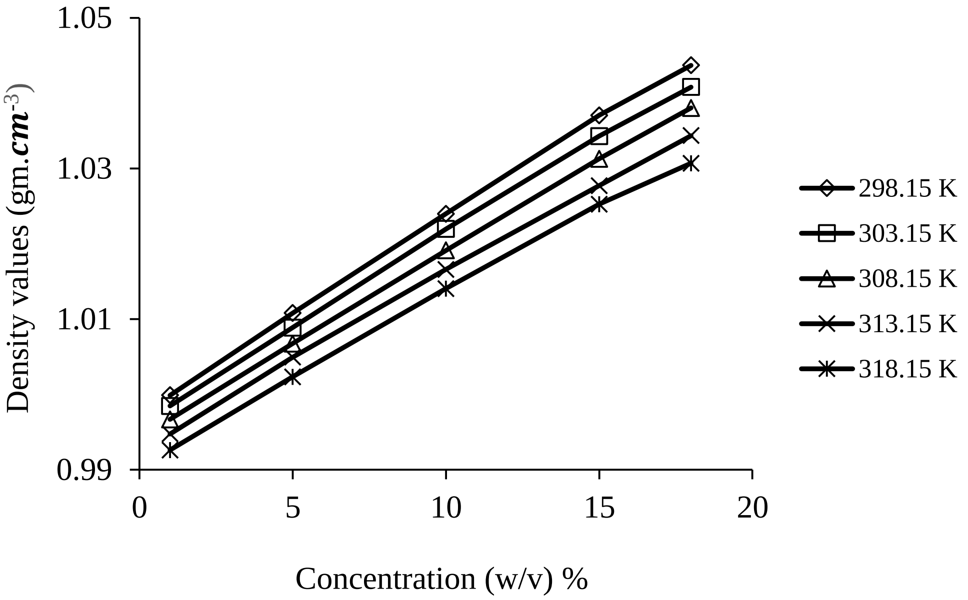


Figure 4.2: Densities, ρ of N- Acetylcysteine in water System at 298.15 to 318.15 K at 5 K interval

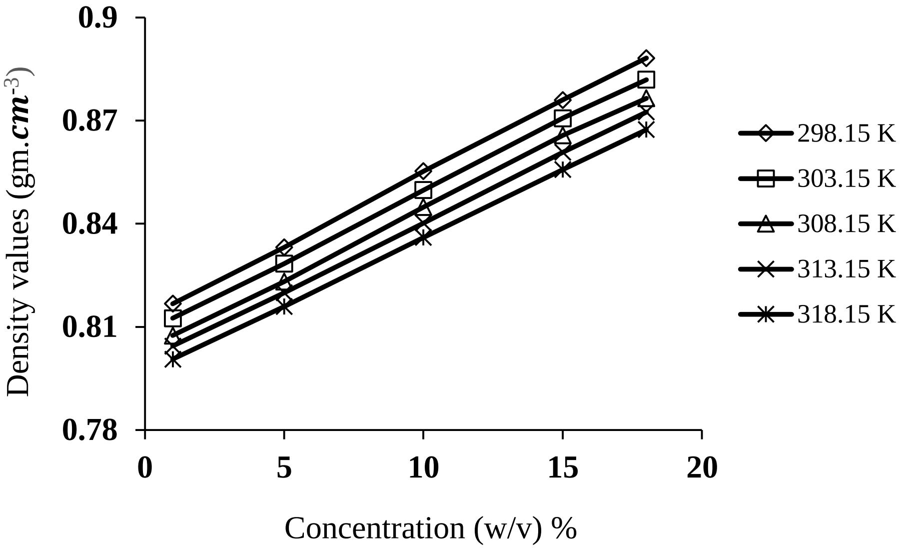


Figure 4.3: Densities, ρ of N-Acetylcysteine in [4:1] ethanol–water System at 298.15 to 318.15 K at 5 K interval

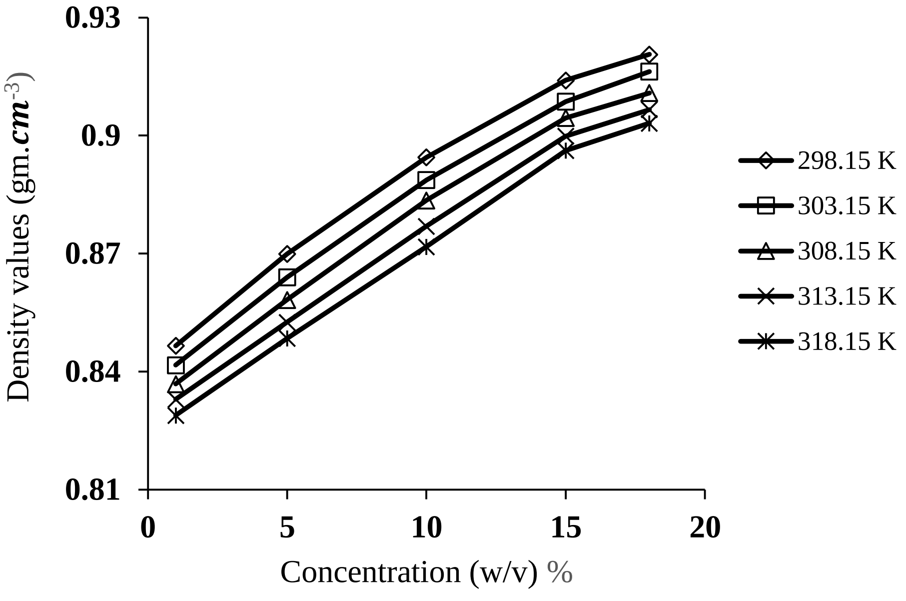


Figure 4.4: Densities, ρ of N-Acetylcysteine in [3:2] ethanol– water System at 298.15 to 318.15 K at 5 K interval

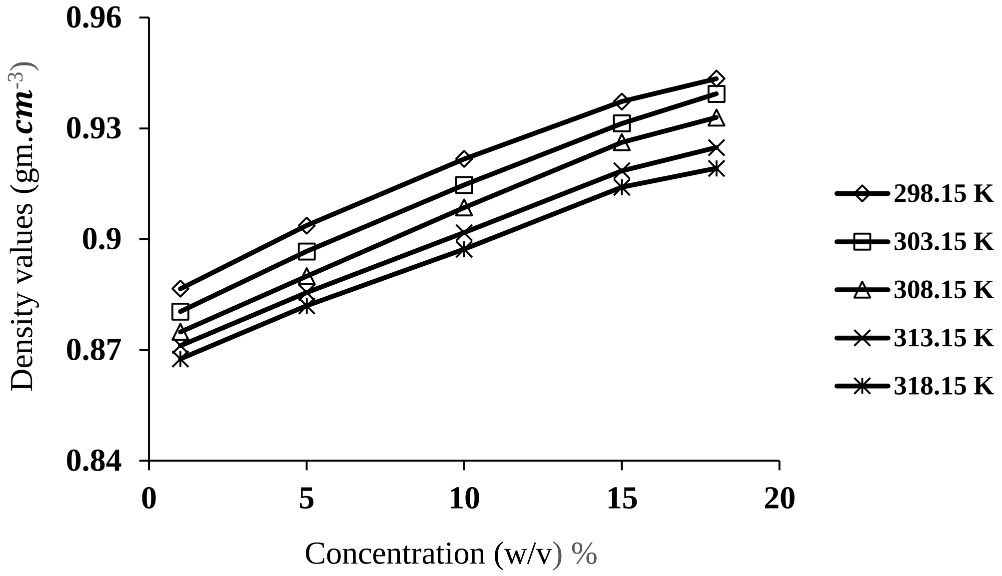


Figure 4.5: Densities, ρ of N-Acetylcysteine in [2:3] ethanol–water System at 298.15 to 318.15 K at 5 K interval

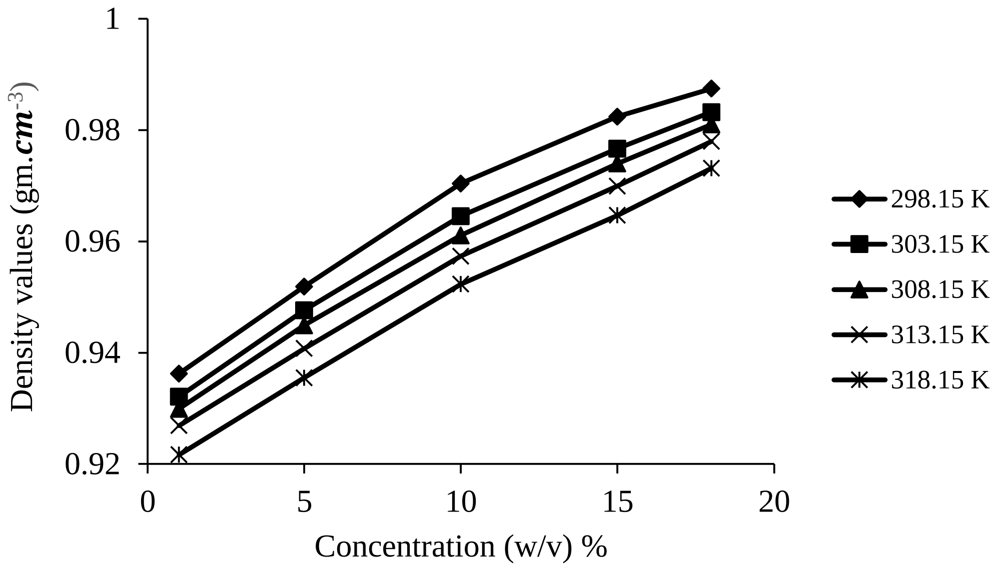


Figure 4.6: Densities, ρ of N-Acetylcysteine in [1:4] ethanol–water System at 298.15 to 318.15 K at 5 K interval

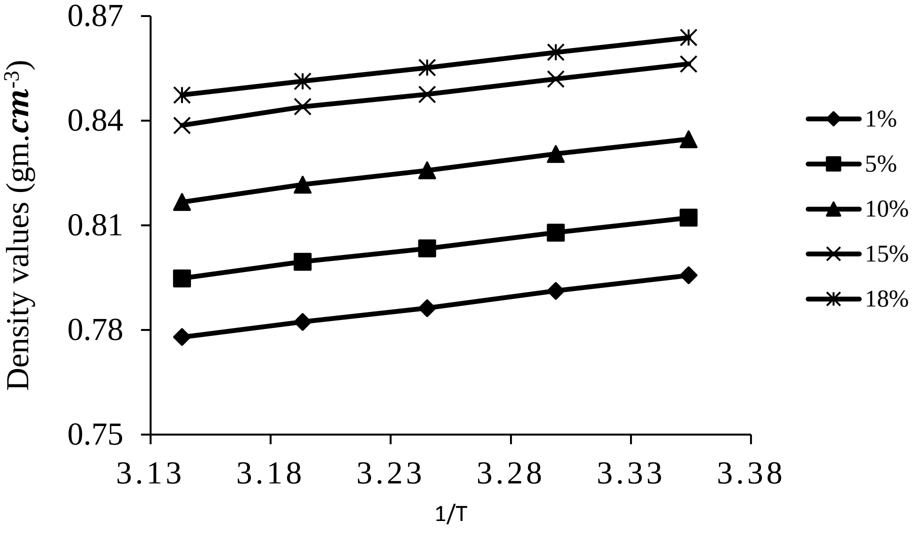


Figure 4.7: Densities, ρ vs $\frac{1}{T}$ of N-Acetylcysteine in ethanol System at 298.15 to 318.15 K at 5 K interval

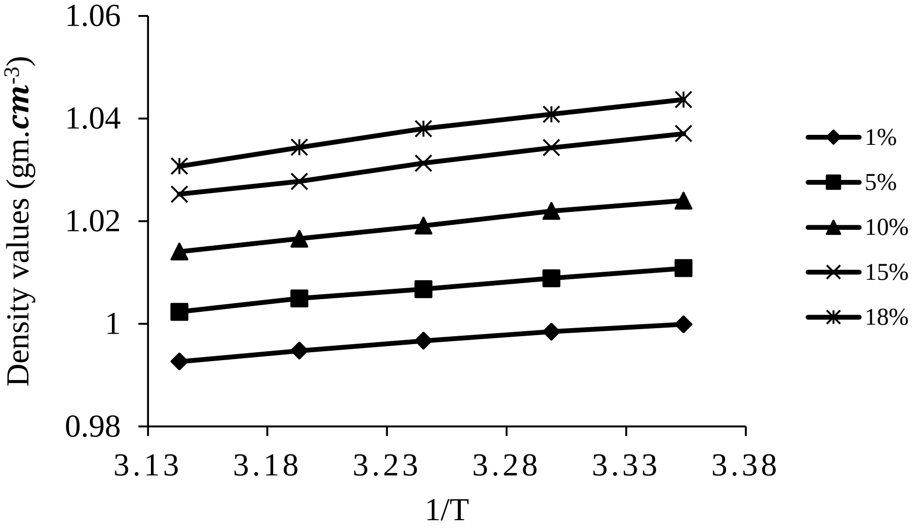


Figure 4.8 Densities, ρ vs $\frac{1}{T}$ of N-Acetylcysteine in water System at 298.15 to 318.15 K at 5 K interval

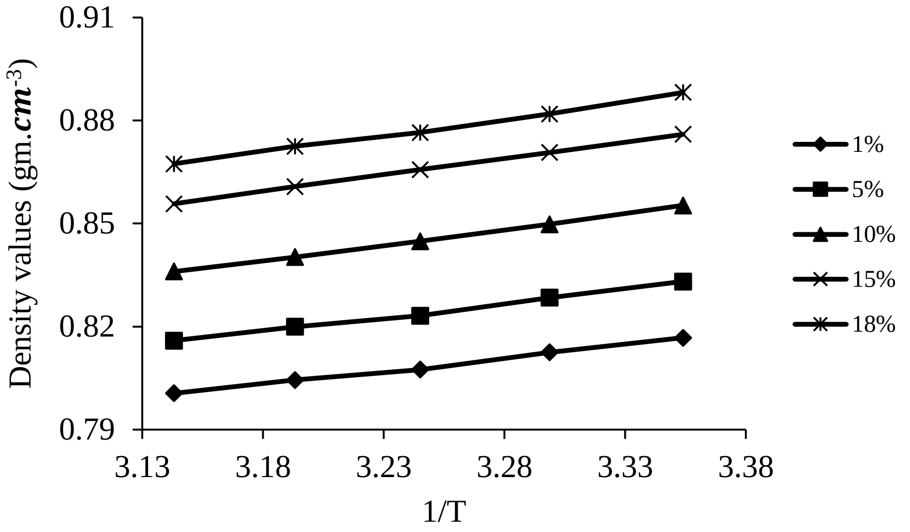


Figure 4.9: Densities, ρ vs $\frac{1}{T}$ of N-Acetylcysteine in [4:1] ethanol–water System at 298.15 to 318.15 K at 5 K interval Density

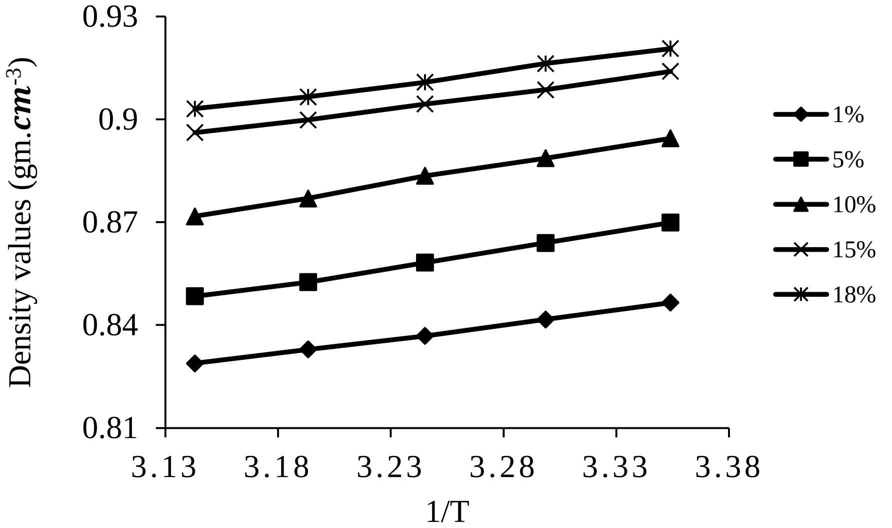


Figure 4.10: Densities, ρ vs $\frac{1}{T}$ of N-Acetylcysteine in [3:2] ethanol–water System at 298.15 to 318.15 K at 5 K interval

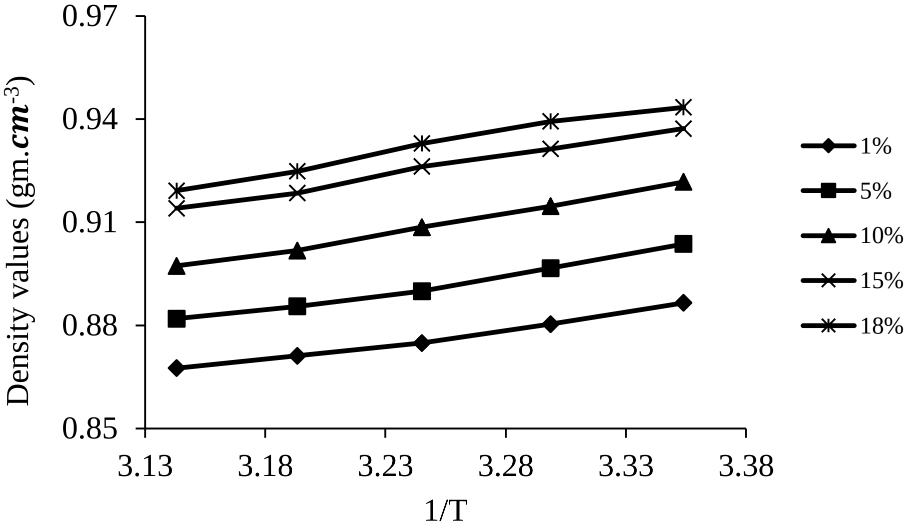


Figure 4.11: Densities, ρ vs $\frac{1}{T}$ of N-Acetylcysteine in [2:3] ethanol–water System at 298.15 to 318.15 K at 5 K interval

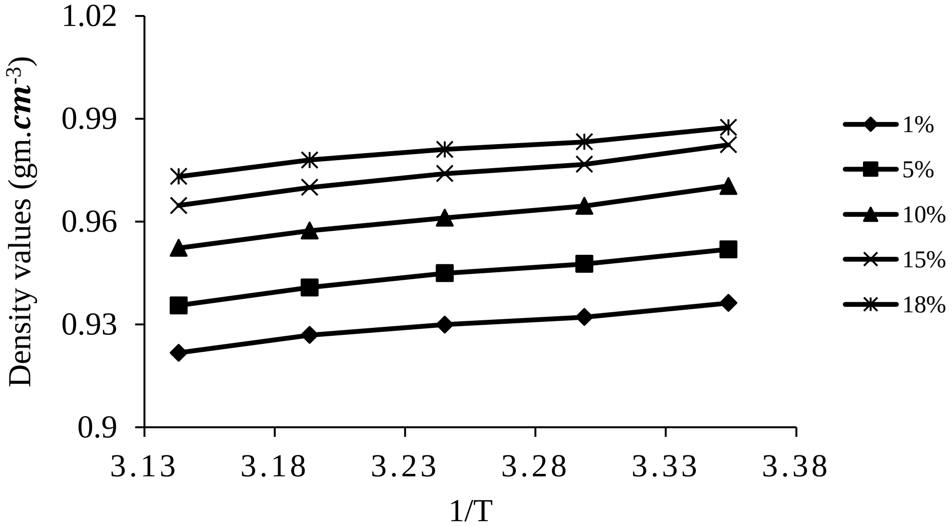


Figure 4.12: Densities, ρ vs $\frac{1}{T}$ of N-Acetylcysteine in [1:4] ethanol–water System at 298.15 to 318.15 K at 5 K interval

4.2.2 Apparent Molar volume

The volumetric properties of NAC in solution can provide useful information in elucidating the interactions which occur in aqueous, ethanolic as well as water–ethanol mixed solutions. NAC possessing both polar and non-polar groups have potential effects on the structure or molar volume of water, ethanol as well as ethanol–water mixed solutions exhibit interactions of particular important applications. Hydrophobic interactions of these groups play an important role in the characteristic reactions and on the stability of many biological systems in water. From a theoretical point of view, the most useful quantities are the limiting values of the apparent molar volume since these values depend only on the intrinsic size of the ion and on ion-solvent interaction. So, the interactions of solutes with water may influence their accession to, and binding with, receptor sites, thus influencing their perception properties. In order to investigate the nature of the solute–solvent interactions of NAC in aqueous ethanolic solution, the apparent molar volume apparent molar volume at infinite dilution were determined. The apparent molar volumes, of NAC in water, ethanol and ethanol–water have been determined at different concentration at 298.15, 303.15, 308.15, 313.15, and 318.15 K by using equation 1.2.8. The values of at different temperature have been shown in Table 4.5-4.6. It is seen that apparent molar volume is dependent upon the concentration of NAC as well as on temperature. The values have been found to be positive throughout the whole concentration range for NAC in all solvent. The apparent molar volumes, of NAC in water, ethanol and ethanol–water were found to be increased with the concentration at all temperatures. These result may be due to the solute-solvent and solute–solute interaction in the solutions as discussed earlier. On the other hand apparent molar volumes were found to be increased with increasing temperature at any concentration of the solution. It may be with increasing temperature the internal energies of the systems increases i.e., increased thermal agitation disturb the more organized structure to less organized structure that causes solute-solvent, solvent-solvent and solute-solute interaction weakened and the resultant is apparent molar volume increases. These show that φ_v values are strongly dependent upon concentration as well as on the temperature but did not follow regular order. The φ_v values are also found to be increased, with the increase of ratio of water in ternary systems. It is clearly seen that, the φ_v values of water–NAC is the highest among binary systems at all the temperatures. Figure 4.13-4.18 showed the stacked line of apparent molar volumes, φ_v versus concentration of NAC in water, ethanol and ethanol – water solutions that represent the trend of the contribution of each apparent molar volume over concentration. From the Figure it is seen that, φ_v values increased square root of concentration. It is seen that apparent molar volumes increased with concentrations in the whole composition range as well as for all the investigated systems but did not follow the regular order. The irregularities may be due to the limitations of the instruments used in the experiments. The apparent molar volumes, φ_v of NAC at all concentration and temperatures in water, ethanol, have been found in order of:

water–NAC > ethanol–NAC

In the ternary systems, ethanol–water–NAC mixture apparent molar volume have found be positive. With increasing the concentration of NAC apparent molar volumes were found to be increased and also increased with increasing temperatures. These data comply the density results as discussed in section 4.2.1. No regular order for apparent molar volume were found with changing ethanol–water ratio.

From the above discussion about apparent molar volume reveals the following characteristics:

- Solute–solvent interaction in the binary systems happened significantly.
- Solute–solvent, solvent–solvent interaction in the ternary systems are significant.
- H–bonding between NAC and solvents, e.g., water and ethanol ensued.
- The addition of NAC in water, ethanol, ethanol–water mixture is accompanied by considerable expansion of apparent molar volume, φ_v are positive and large in magnitude.
- φ_v is increased with increasing temperature i.e., temperature effect on φ_v is quite significant.
- With increasing concentration of NAC, φ_v is increased i.e., concentration effect is also significant.
- In ternary systems with the increase of the ratio of water the φ_v values have been increased.

Table 4.5: Apparent molar volume (cm^3.mol^{-1}), φ_v of NAC in ethanol and water systems at 298.15 to 318.15 K at 5 K interval

Name of the system	Conc. (w/v)%	φ_v (cm^3.mol^{-1})				
		298.15 K	303.15 K	308.15 K	313.15 K	318.15 K
ethanol –NAC	1	76.77	78.35	86.12	87.93	92.00
	5	112.61	112.66	113.11	113.31	116.20
	10	113.10	113.30	114.29	115.24	117.56
	15	114.59	115.09	115.53	115.56	117.82
	18	121.26	121.72	122.19	122.79	123.17
water –NAC	1	116.31	116.79	119.93	122.35	124.84
	5	118.45	120.39	122.29	122.52	124.82
	10	119.50	120.70	122.93	124.36	125.49
	15	119.98	121.63	123.36	125.53	126.30
	18	121.23	122.74	124.02	125.95	127.75

Table 4.6: Apparent molar volume ($cm^3.mol^{-1}$), φ_v of N-Acetylcysteine in [4:1], [3:2], [2:3], [1:4] ethanol–water System at 298.15 to 318.15 K at 5 K interval

Name of the system	Conc./ (w/v)%	φ_v ($cm^3.mol^{-1}$)				
		298.15 K	303.15 K	308.15 K	313.15 K	318.15 K
[4:1] ethanol–water –NAC	1	74.49	75.48	78.90	80.14	81.39
	5	110.01	112.70	114.85	116.19	117.64
	10	111.08	114.24	115.04	118.80	120.17
	15	113.36	115.41	116.27	119.32	121.60
	18	114.37	117.32	118.63	120.17	122.27
[3:2] ethanol– water –NAC	1	79.28	82.07	89.59	95.68	98.33
	5	80.50	85.36	90.92	99.62	100.62
	10	89.62	92.08	93.92	100.21	103.17
	15	99.18	100.50	100.66	102.43	102.53
	18	107.87	108.00	109.67	110.83	110.82
[2:3] ethanol–water –NAC	1	56.10	97.76	111.70	115.13	115.42
	5	96.21	107.96	115.80	119.38	119.87
	10	107.35	113.59	116.69	123.22	125.47
	15	114.23	117.15	118.24	123.89	125.49
	18	119.71	120.39	122.77	128.02	130.69
[1:4] ethanol–water –NAC	1	102.96	105.92	109.40	113.79	114.49
	5	105.52	107.17	110.06	115.16	115.95
	10	107.69	111.72	114.63	116.65	116.97
	15	116.05	118.84	120.01	121.82	122.58
	18	120.96	121.93	122.49	123.12	123.45

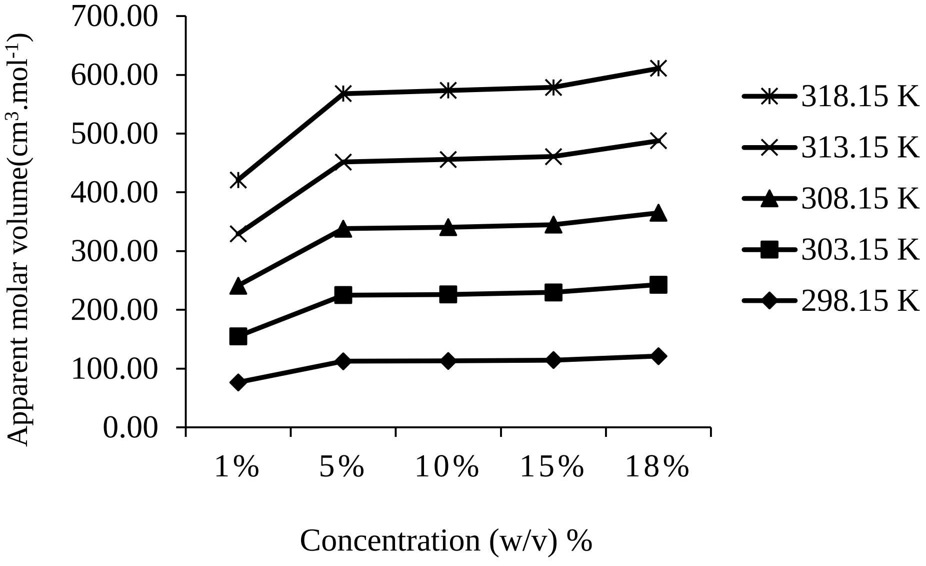


Figure 4.13: Apparent molar volume, φ_v of N-Acetylcysteine in ethanol System at 298.15 to 318.15 K at 5 K interval

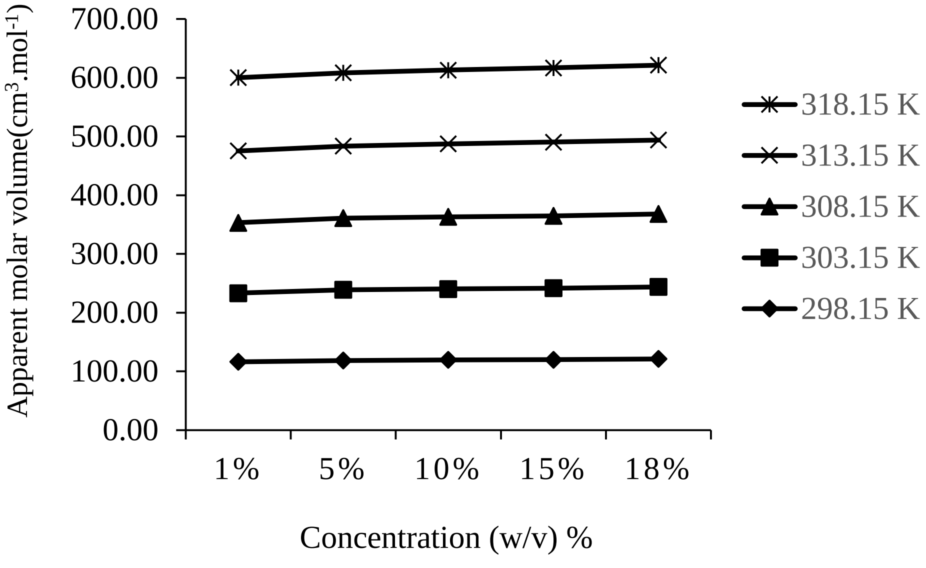


Figure 4.14: Apparent molar volume, φ_v of N-Acetylcysteine in water System at 298.15 to 318.15 K at 5 K

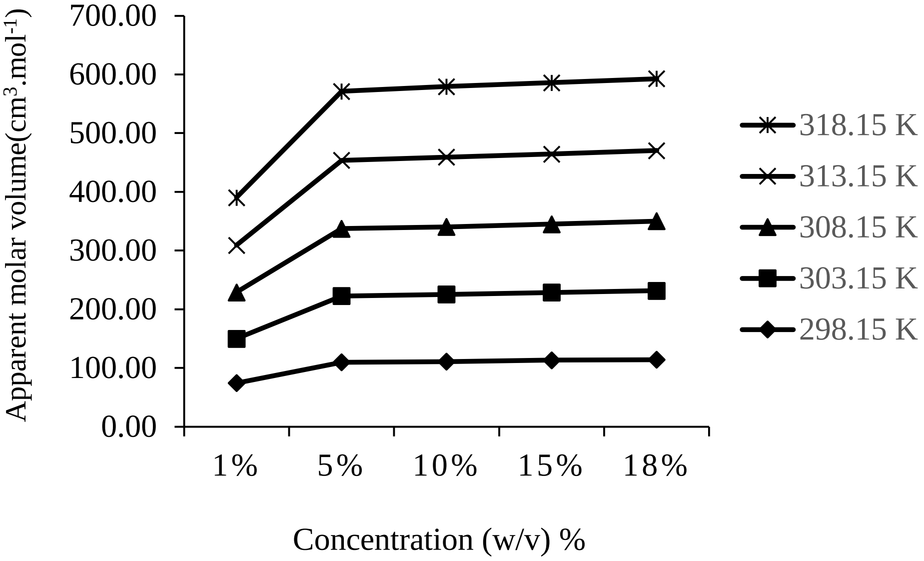


Figure 4.15: Apparent molar volume, φ_v of N-Acetylcysteine in [4:1] ethanol–water System at 298.15 to 318.15 K at 5 K interval

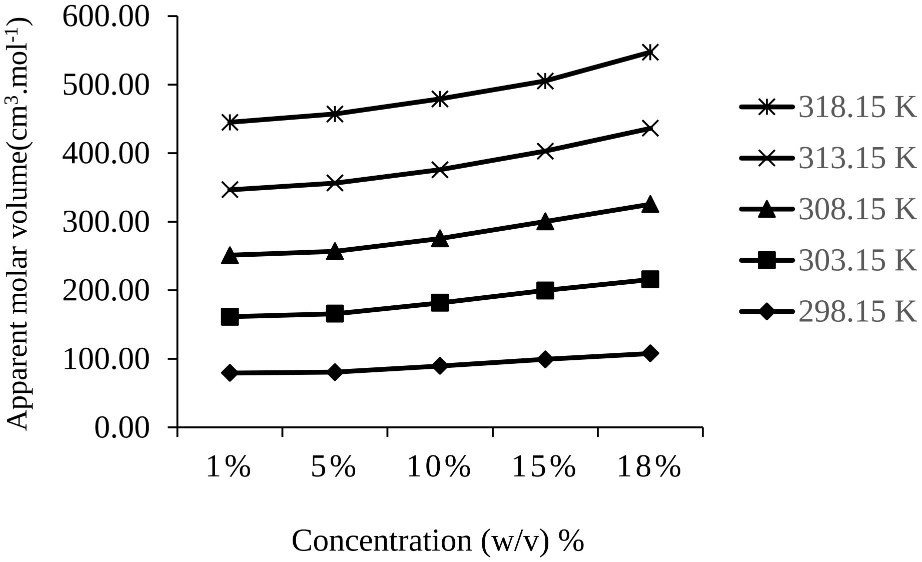


Figure 4.16: Apparent molar volume, φ_v of N- Acetylcysteine in [3:2] ethanol–water System at 298.15 to 318.15 K at 5 K interval

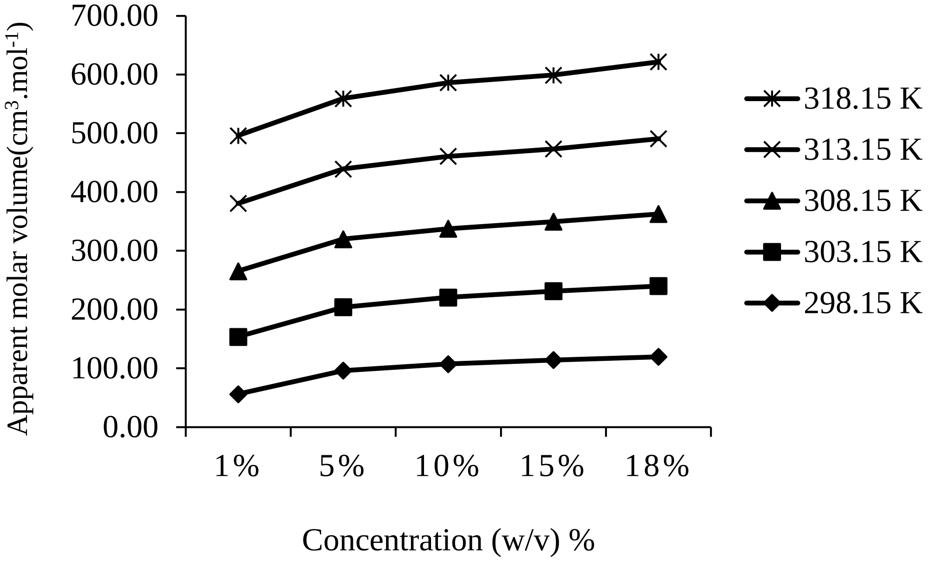


Figure 4.17: Apparent molar volume, φ_v of N- Acetylcysteine in [2:3] ethanol–water System at 298.15 to 318.15 K at 5 K interval

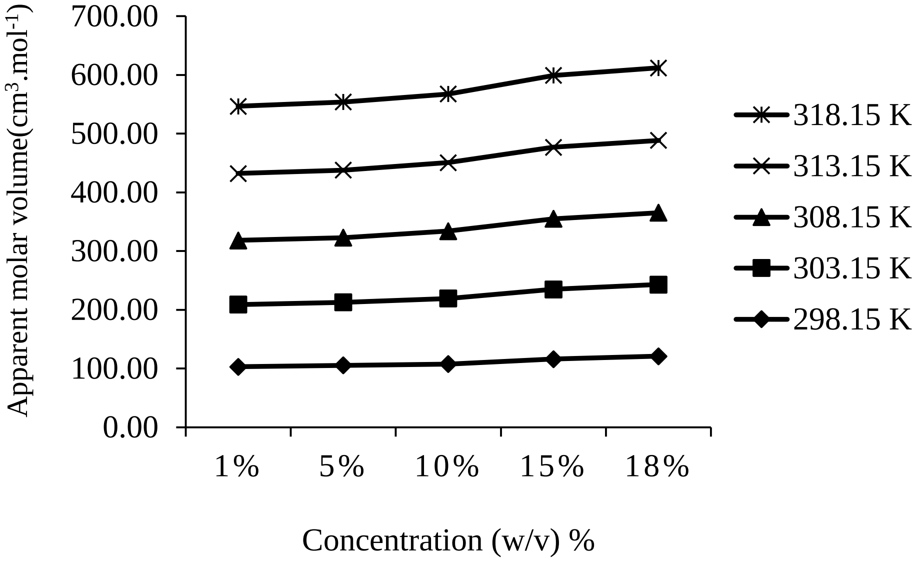


Figure 4.18: Apparent molar volume, φ_v of N-Acetylcysteine in [1:4] ethanol–water System at 298.15 to 318.15 K at 5 K interval

4.2.3 Apparent molar volume at infinite dilution

φ_v^0 values can be used for understanding solute–solvent and S_V values for solute–solute or ion–ion interactions. The apparent molar volumes at infinite dilution φ_v^0 values of NAC in water, ethanol, ethanol–water mixtures are tabulated in Table 4.7. The results can be revealed as a function of both temperature and the structure of NAC. The φ_v^0 values of NAC reflect the true value of NAC at the specified temperatures. Apparent molar volumes at infinite dilution were computed from intercept of the plot between φ_v and $C^{1/2}$ as per following Masson equation 1.2.14.

$$\varphi_v = \varphi_v^0 + S_v\sqrt{c}$$

Where, S_V is measure of ion–ion interactions among solutes. Variation of apparent molar volume with square root of concentration of NAC for all systems have been evaluated. We have computed two parameters, φ_v and $C^{1/2}$ former is the experimental slope of graph between φ_v and $C^{1/2}$ and is a function of ion–ion interactions and later is intercept of this graph and is solute–solvent interaction parameter in solution and it is apparent molar volume at infinite dilutions. Table 4.7 presents values of experimental slopes (S_V) and intercepts φ_v^0 for different systems. Sign of S_V gives information about the structural influence of solute on solvent system that is, whether solute acts as a structure promoting or structure breaker [44, 45] of solvent or solvent mixture. Investigated systems showed small positive values for S_V which indicate that the solvation process involve strong interaction but not pure ionic. It is seen that φ_v^0 increased with increasing temperature which is quite logical as agitation increased at higher temperatures. These values are expected to provide information on solute-solvent interactions, as solute-solute interaction can be assumed to be eliminated at infinite dilution. It is mentioned here that in case of few systems apparent molar volumes deviated a lot especially at 0.06 $mol.L^{-1}$ concentration. From the experimentations my presumption is that it is not the system's behavior but for the limitations of the instruments used and also my personal error. So in computing φ_v^0 those values were ignored.

Table 4.7: Apparent molar volume (cm^3.mol^{-1}), φ_v^0 at infinite dilution of NAC in ethanol, water, [4:1], [3:2], [2:3], [1:4] ethanol–water systems at 298.15 to 318.15 K at 5 K interval

Temperature (K)	φ_v^0 (cm^3.mol^{-1})					
	NAC–ethanol	NAC–water	[4:1] ethanol –water–NAC	[3:2] ethanol – water–NAC	[2:3] ethanol –water–NAC	[1:4] ethanol –water–NAC
298.15	73.1168	115.0671	72.1643	66.1716	44.6045	95.2832
303.15	74.4706	115.6825	73.2406	71.2144	91.7642	98.4785
308.15	82.3045	119.1195	77.1176	80.9570	108.7006	103.1746
313.15	84.0712	120.6286	78.1479	91.0273	111.3519	109.6102
318.15	89.1555	123.5213	78.9722	94.4203	110.7716	110.4508

Table 4.8: S_v parameter of N-Acetylcysteine in ethanol, water, [4:1], [3:2], [2:3], [1:4] ethanol–water System at 298.15 to 318.15 K at 5 K interval

Temperature (K)	Ethanol –NAC	Water–NAC	[4:1] ethanol –water–NAC	[3:2] ethanol –water–NAC	[2:3] ethanol –water–NAC	[1:4] ethanol –water–NAC
298.15	48.1183	5.6082	45.2609	34.9866	75.3678	21.3794
303.15	47.0106	6.6397	47.0589	31.1830	27.3080	20.3813
308.15	38.9196	4.7186	44.0385	22.2771	11.6151	16.9128
313.15	37.4573	4.8908	45.6523	14.9407	14.7277	11.8366
318.15	33.6976	3.2277	46.8539	12.0786	17.5714	11.4732

4.2.4 Apparent molar expansivity

The parameter that measures the variation of volume with temperature is the apparent molar expansivity, (φ_E) which was defined by the equation 1.2.20. These values of molar expansivities at infinite dilution (φ_E^0) are shown in Table 4.9. The expansivities values at infinite dilution are positive. Positive values indicate that, on heating some NAC molecules may be released from the solvation layer of ion. It may also be conferred that the positive (φ_E^0) values may be originated from the hydrophobic character and steric effect of the NAC. As a whole there is a hydrophilic/hydrophobic balance among the solute and solvent molecules and the molar expansivities at infinite dilution varied from the range of 0.0979 to 2.7199, quite acceptable.

Table 4.9: `Apparent molar expansivity ($cm^3.mol^{-1}.K^{-1}$), φ_E^0 at infinite dilution of NAC in ethanol, water, [4:1], [3:2], [2:3], [1:4] ethanol–water–NAC at 298.15 to 318.15 K at 5 K interval

Conc./ (w/v)%	φ_E^0 ($cm^3.mol^{-1}.K^{-1}$)					
	ethanol –NAC	water– NAC	[4:1] ethanol–water–NAC	[3:2] ethanol–water–NAC	[2:3] ethanol–water–NAC	[1:4] ethanol–water–NAC
1	0.8008	0.4524	0.3694	1.0341	2.7199	0.6191
5	0.1563	0.2971	0.3749	1.0899	1.1748	0.5773
10	0.2174	0.3129	0.4550	0.7043	0.9175	0.4700
15	0.1387	0.3307	0.4078	0.1724	0.5853	0.3209
18	0.0979	0.3250	0.3729	0.1745	0.5919	0.1235

4.3 Viscometric Properties

With enormous medicinal and biological applications of NAC in human body, its viscometric investigation in versatile solvent water, in common organic solvent ethanol and also in ethanol–water mixed solvents might be interesting. Alcohol–water mixtures are very important systems exhibiting properties that are of great interest in physics, chemistry and biology. So viscometric behavior of NAC in ethanol–water mixture is also fascinating. The viscosities, η of NAC solutions in ethanol, water and ethanol–water at 298.15, 303.15, 308.15, 313.15, and 318.15 K over a concentration range of 1-18% (w/v) were studied. Results are tabulated in Table 4.10-4.12. The viscosities of the pure ethanol at the experimented temperatures are shown in the Table 4.1. The values of η of NAC, in ethanol, water and ethanol–water systems, increased with the increase of concentration. At the same time it is seen that the viscosities values decrease considerably with temperature at a constant temperature. With the increase of temperature the internal energy of the system is increased and the solute-solvent interaction may be depleted. The increase of η values of NAC with concentration can be attributed to the increase in both solute–solvent, solvent–solvent and solute–solute interactions with concentration. The wide range of dissolution of NAC in water, ethanol and water–ethanol mixture might have intriguing aspects are consequence of the great ability of both water and alcohol to make hydrogen bonds. Even alcohol, water and alcohol–water systems can have two hydrogen-bonded structures corresponding to the two possible heterodimers (or isomers) where alcohol is a proton acceptor, or a proton donor. The existence of these two isomers is very easy to understand but the relative strength of the two possible conformations is more difficult to ascertain. In case of alcohols, the basic solubility rule that like dissolves like is a bit more complex. Each alcohol consists of a carbon chain (always nonpolar) and a –OH group (which is polar). For ethanol, the chemical formula looks like this: ethanol, C_2H_5OH has aliphatic carbon chain and a –OH group. As water is polar it attracts –OH group. Carbon chain on the other hand as nonpolar is repelled. Solubility of alcohols is therefore determined by the stronger of the two forces. Because of the strength of the attraction of the –OH group, ethanol is completely miscible. They dissolve in water in any amount. On the other hand NAC contains two polar groups –COOH and CH_3CONH– . It also contains almost nonpolar –SH group. Using this NAC make strong interactions in water–NAC or ethanol–NAC binary and water–ethanol–NAC ternary systems which is responsible to occur strong cohesive force and change the viscosity a lot.

The variation of viscosities with concentration of NAC in ethanol, water and ethanol–water has been investigated at various temperatures and is shown in Figure 4.19-4.4.24. The following characteristic features of viscosity are observed:

i) Viscosities increased sharply with increasing the concentration NAC.
ii) Viscosities decreased with the rise of temperature.
iii) The viscosity maxima follow the order:

[1:4] ethanol–water–NAC > [2:3] ethanol–water–NAC > [3:2] ethanol–water–NAC > [4:1] ethanol–water–NAC > ethanol–NAC > water–NAC

The intense change in viscosity of NAC in different solvents may make a significant contribution to thermodynamic properties of the solution, such as enthalpy, entropy, and other properties in solution.

Table 4.10: Viscosities (mPa.S), η of N- Acetylcysteine in ethanol and water System at 298.15 to 318.15 K at 5 K interval

Name of the system	**Conc./ (w/v)%**	η (mPa.S)				
		298.15 K	**303.15 K**	**308.15 K**	**313.15 K**	**318.15 K**
ethanol –NAC	1	1.13747	1.03394	0.94018	0.85795	0.78937
	5	1.21787	1.11364	1.01060	0.92500	0.84537
	10	1.36105	1.23834	1.11891	1.03315	0.93614
	15	1.45519	1.31270	1.19841	1.09360	1.00403
	18	1.54305	1.40572	1.27984	1.16008	1.06820
water– NAC	1	0.90962	0.81366	0.73079	0.66439	0.60175
	5	0.98692	0.87825	0.78744	0.70968	0.64497
	10	1.09216	0.96537	0.86150	0.77534	0.69922
	15	1.23019	1.07928	0.95641	0.85063	0.76353
	18	1.32741	1.16563	1.02456	0.91006	0.81578

Table 4.11: Viscosities (mPa.S), η of [4:1], [3:2], [2:3], [1:4] ethanol–water System at 298.15 to 318.15 K at 5 K interval

Name of the system	η (mPa.S)				
	298.15K	303.15K	308.15K	313.15K	318.15K
[4:1] ethanol–water	1.3871	1.2365	1.1201	0.9681	0.8694
[3:2] ethanol– water	1.6251	1.4913	1.3439	1.1966	1.0451
[2:3] ethanol– water	2.1113	1.8235	1.6505	1.4620	1.3132
[1:4] ethanol–water	2.3352	1.9633	1.7407	1.5532	1.3876

Table 4.12: Viscosities (mPa.S), η of NAC in [4:1], [3:2], [2:3], [1:4] ethanol–water System at 298.15 to 318.15 K at 5 K interval

Name of the system	**Conc./ (w/v)%**	η (mPa.S)				
		298.15 K	**303.15 K**	**308.15 K**	**313.15 K**	**318.15 K**
[4:1] ethanol–water–NAC	1	1.43450	1.24945	1.11495	0.97100	0.85929
	5	1.56606	1.37850	1.23009	1.06302	0.95040
	10	1.75032	1.54491	1.36516	1.18401	1.05773
	15	2.22262	1.91905	1.69701	1.44404	1.26385
	18	2.46917	2.12750	1.86494	1.61420	1.40099
[3:2] ethanol–water–NAC	1	1.70002	1.51721	1.35145	1.21708	1.09077
	5	1.84758	1.63985	1.46012	1.28841	1.12083
	10	2.01977	1.78832	1.58441	1.41778	1.23769
	15	2.20462	1.93895	1.71278	1.51800	1.28965
	18	2.35333	2.05588	1.83274	1.62622	1.41330
[2:3] ethanol–water–NAC	1	2.13742	1.87281	1.66900	1.49653	1.34058
	5	2.27624	1.96998	1.75679	1.56132	1.39216
	10	2.45401	2.1096	1.86536	1.64178	1.46263
	15	2.61736	2.26356	2.00073	1.76974	1.57582
	18	2.76373	2.37607	2.05529	1.81720	1.61258
[1:4] ethanol–water–NAC	1	2.33526	1.96336	1.74076	1.55327	1.38769
	5	2.45535	2.16515	1.92536	1.71107	1.53598
	10	2.63289	2.33621	2.07665	1.83773	1.62400
	15	2.78151	2.46420	2.19083	1.94356	1.72447
	18	2.91042	2.58045	2.27630	2.01197	1.79477

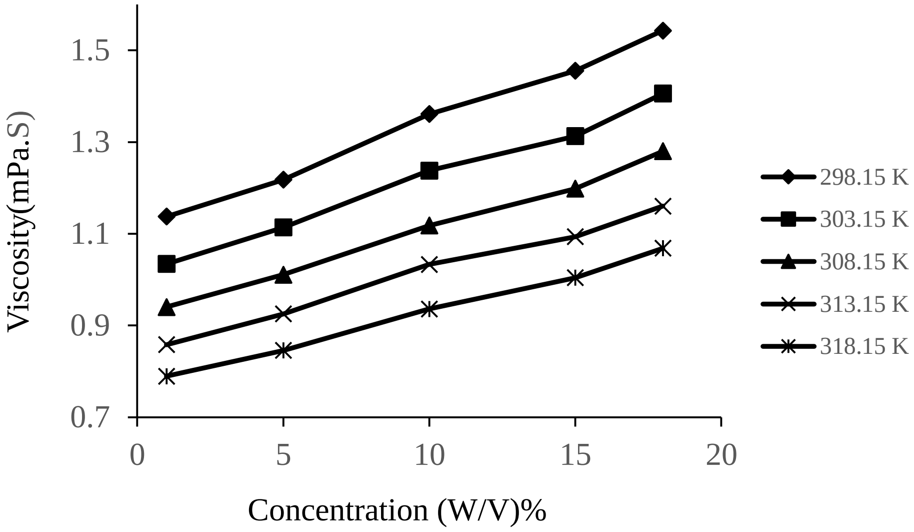


Figure 4.19: Viscosities (η), of N-Acetylcysteine in ethanol System at 298.15 to 318.15 K at 5 K interval

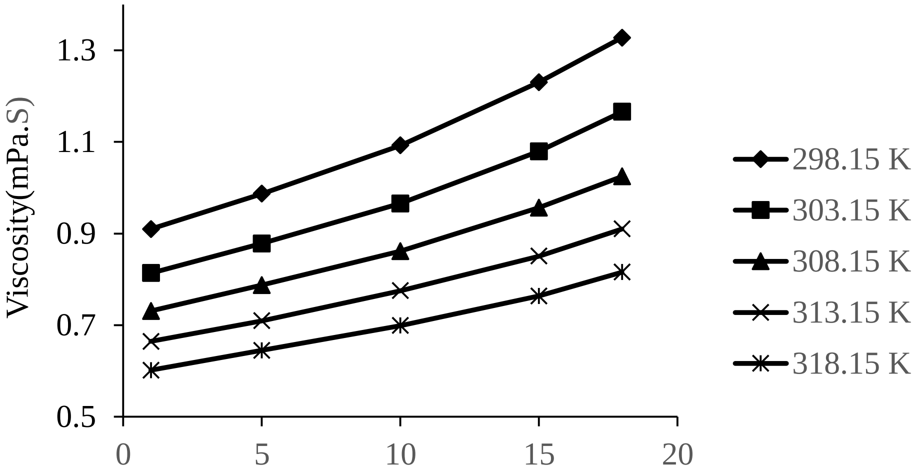


Figure 4.20: Viscosities (η), of N-Acetylcysteine in water System at 298.15 to 318.15 K at 5 K interval

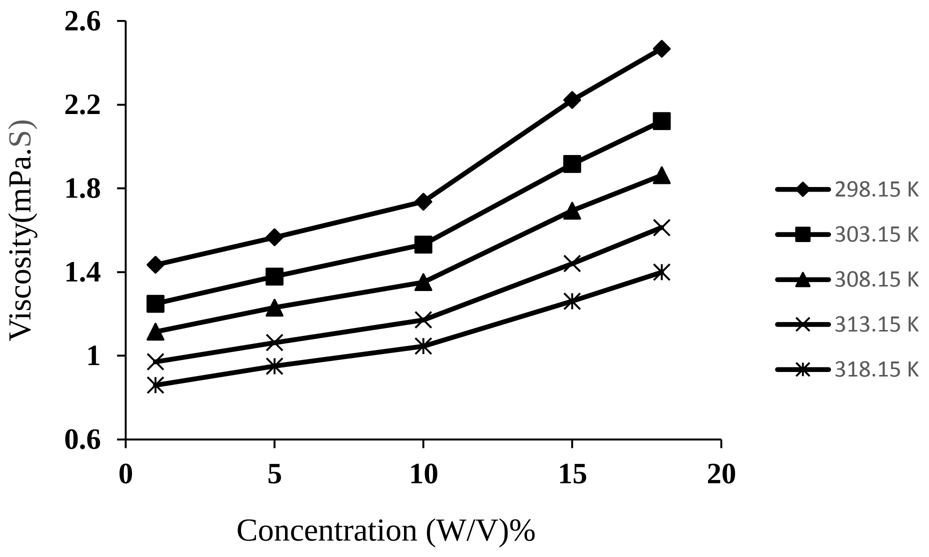


Figure 4.21: Viscosities (η), of N-Acetylcysteine [4:1] ethanol–water System at 298.15 to 318.15 K at 5 K interval

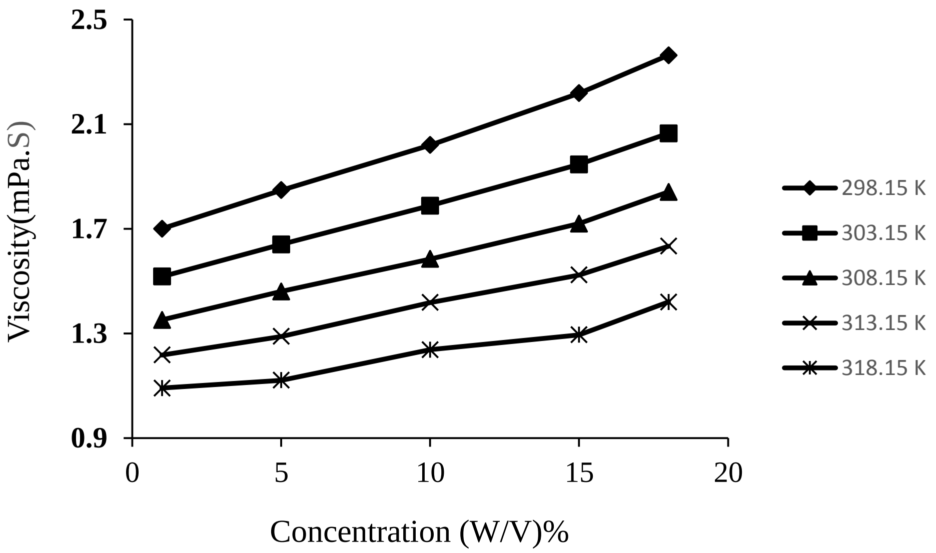


Figure 4.22: Viscosities (η), of N-Acetylcysteine [3:2] ethanol–water System at 298.15 to 318.15 K at 5 K interval

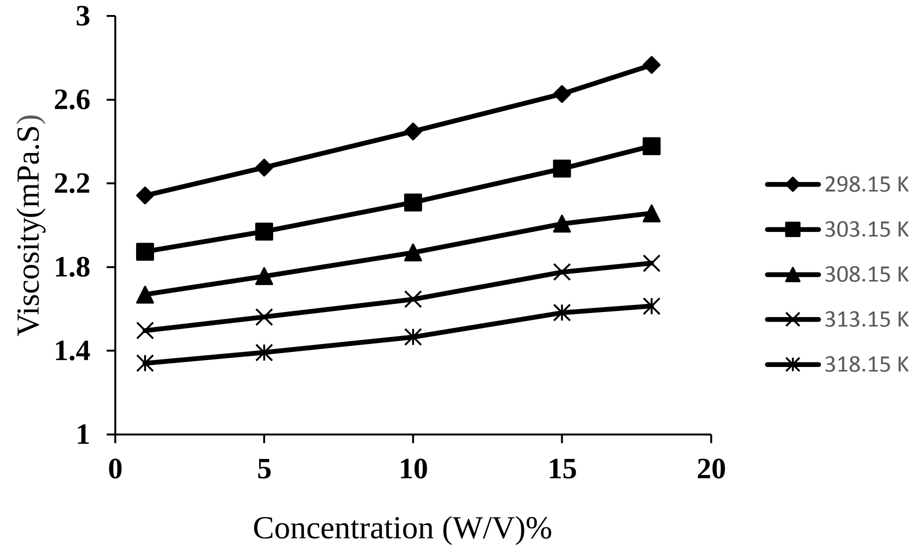


Figure 4.23: Viscosities (η), of N-Acetylcysteine [2:3] ethanol–water System at 298.15 to 318.15 K at 5 K interval

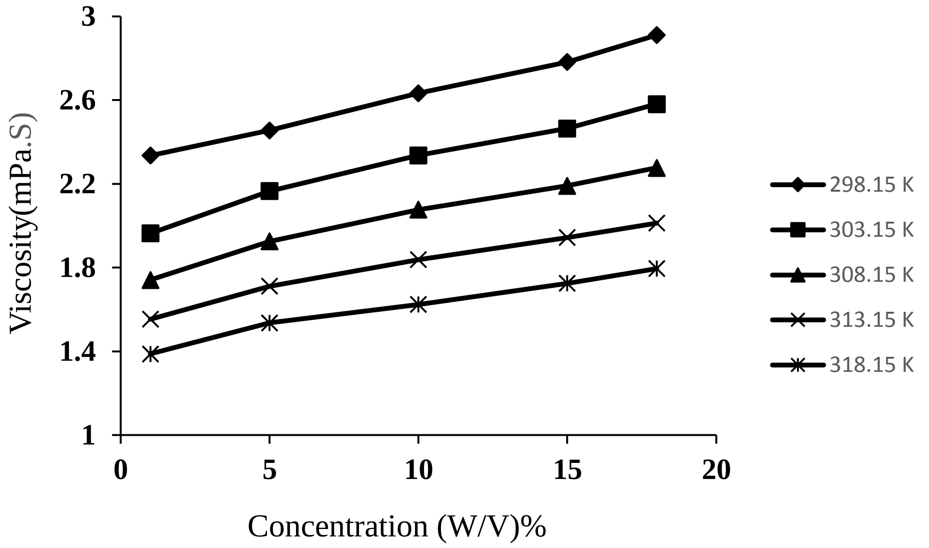


Figure 4.24: Viscosities (η), of N-Acetylcysteine [1:4] ethanol–water System at 298.15 to 318.15 K at 5 K interval

4.4 Thermodynamics Properties

Alcohol–NAC, water–NAC and alcohol–water–NAC are considered to be very important systems exhibiting properties that are of great interest in many biological and medicinal applications. These include several thermodynamic properties such as, free energy, entropy, enthalpy, etc. Thermodynamic properties, change of free energy, ΔG^*, change of enthalpy, ΔH^*, change of entropy, ΔS^* for viscous flow have been calculated from viscometric data. Gibbs free energy is a thermodynamic function and the energy of the system which is ready to work. The Gibbs free energy is used when considering processes that occur under constant pressure and temperature conditions whereas the Helmholtz free energy is used when considering processes that occur under constant volume and temperature conditions. For a process that occurs at constant temperature and pressure, spontaneity can be determined using the change in Gibbs free energy, which is given by: where, the sign of ΔG depends on the signs of the changes in enthalpy (ΔH) and entropy (ΔS), as well as on the absolute temperature (T).

In cases where ΔG is:

- Negative, the process is spontaneous and may proceed in the forward direction as written.
- Positive, the process is non-spontaneous as written, but it may proceed spontaneously in the reverse direction.
- Zero, the process is at equilibrium, with no net change taking place over time.

The ΔG^*, values are positive for all the studied systems (Alcohol–NAC, water–NAC and Alcohol–water–NAC) indicate that studied systems are non-spontaneous for the flow process as shown in Table 4.13 and 4.14 and it is spontaneous in the reverse direction. The positive free energy change, ΔG^* for viscous flow may be interpreted by Furth model [75] which states that kinetic species involved in forming holes in the investigated solution systems may be stated by the work is required in forming the holes against surface tension of the solution. Positive ΔG^* values also explain the interstitial incorporation, solute–solvent interaction that render the binary and ternary systems are more structured.

Enthalpy is the thermodynamic quantity equivalent to the total heat content of a system. It is defined as the sum of internal energy of a system and the product of the pressure and volume of the system or pressure-volume work. Internal energy is the sum of translational energy, rotational energy, vibrational energy and the kinetic energy of a matter. The change in enthalpy is the sum of the change in the internal energy and the work done. Entropy is a measure of disorder or randomness of a system. In other words, it's a measurement of the degree of randomness of energy in a system. An ordered system has low entropy. A disordered system has high entropy.

The set of rules can be used to determine four distinct cases by examining the signs of the ΔS and ΔH.

- When $\Delta S > 0$ and $\Delta H < 0$, the process is always spontaneous as written.
- When $\Delta S < 0$ and $\Delta H > 0$, the process is never spontaneous, but the reverse process is always spontaneous.
- When $\Delta S > 0$ and $\Delta H > 0$, the process will be spontaneous at high temperatures and non-spontaneous at low temperatures.
- When $\Delta S < 0$ and $\Delta H < 0$, the process will be spontaneous at low temperatures and non-spontaneous at high temperatures.
- For the latter two cases, the temperature at which the spontaneity changes will be determined by the relative magnitudes of ΔS and ΔH.

The change enthalpy, ΔH* values are positive for all the studied system as shown in Table 4.15-4.16. The positive ΔH values indicate that work has to be done for all the investigated systems. That is, the viscous flow is not thermodynamically favored for the systems studied. The, change entropy, ΔS* of the investigated systems are shown in Table 4.15-4.16. The ΔS* values are positive for all the systems studied except ethanol–NAC system. This means that except ethanol–NAC system other binary and ternary systems are random that those of the pure one. Here one point may be remarked that, as $\Delta S > 0$ and $\Delta H > 0$, so the process (except ethanol–NAC systems) will be spontaneous at high temperatures and non-spontaneous at low temperatures. In case of my studied temperatures these systems were found to be non-spontaneous. For ethanol–NAC system $\Delta S < 0$ and $\Delta H > 0$, the process is never spontaneous, but the reverse process is always spontaneous. In fact, change enthalpy, ΔH* and change entropy, ΔS* are derived from viscosity and molar volume as secondary derived data. It is also mentioned that the instrumental limitations during the experiments may hamper of the data of investigated system in both binary and ternary system. So some irregularities as well as some ambiguity may be present in change enthalpy, ∆H* and change entropy, ∆S* values.

Table 4.13: Free energy, ∆G* of N–Acetylcysteine in ethanol and water System at 298.15 to 318.15 K at 5 K interval

Name of the system	**Conc./ (w/v)%**	∆G* *KJ.mol^{-1}*				
		298.15 K	**303.15 K**	**308.15 K**	**313.15 K**	**318.15 K**
ethanol –NAC	1	15.8123	15.8510	15.8840	15.9165	15.9646
	5	15.9816	16.0382	16.0690	16.1124	16.1459
	10	16.2571	16.3045	16.3274	16.4002	16.4156
	15	16.4229	16.4527	16.5057	16.5483	16.6008
	18	16.5682	16.6252	16.6741	16.7019	16.7647
water–NAC	1	14.6794	14.6482	14.6187	14.6126	14.5893
	5	14.8816	14.8407	14.8100	14.7843	14.7728
	10	15.1328	15.0791	15.0402	15.0147	14.9864
	15	15.4278	15.3602	15.3080	15.2560	15.2191
	18	15.6163	15.5542	15.4844	15.4318	15.3942

Table 4.14: Free energy, ΔG* of NAC in [4:1], [3:2], [2:3], [1:4] ethanol–water system at 298.15 to 318.15 K at 5 K interval

Name of the system	**Conc./ (w/v)%**	ΔG* *KJ.mol^{-1}*				
		298.15 K	**303.15 K**	**308.15 K**	**313.15 K**	**318.15 K**
[4:1] ethanol–water–NAC	1	15.8086	15.7280	15.7009	15.6005	15.5317
	5	16.0261	15.9769	15.9527	15.8363	15.7982
	10	16.2823	16.2428	16.1942	16.0889	16.0524
	15	16.8940	16.8073	16.7724	16.6278	16.5460
	18	17.1537	17.0638	17.0165	16.9214	16.8222
[3:2] ethanol–water–NAC	1	16.2296	16.2186	16.1938	16.1886	16.1626
	5	16.4359	16.4145	16.3919	16.3369	16.2345
	10	16.6568	16.6329	16.6012	16.5860	16.4968
	15	16.8890	16.8456	16.8110	16.7730	16.6150
	18	17.0465	16.9954	16.9856	16.9547	16.8596
[2:3] ethanol–water–NAC	1	16.8028	16.7504	16.7345	16.7268	16.7081
	5	16.9531	16.8768	16.8658	16.8371	16.8079
	10	17.1342	17.0493	17.0251	16.9748	16.9444
	15	17.3088	17.2345	17.2078	17.1736	17.1462
	18	17.4362	17.3513	17.2700	17.2345	17.1990
[1:4] ethanol–water–NAC	1	17.0166	16.8683	16.8423	16.8236	16.7994
	5	17.1409	17.1149	17.1006	17.0755	17.0680
	10	17.3139	17.3065	17.2943	17.2615	17.2154
	15	17.4500	17.4409	17.4315	17.4072	17.3741
	18	17.5623	17.5571	17.5295	17.4973	17.4798

Table 4.15: Change of Enthalpy, ΔH* and Entropy, ΔS*of N–Acetylcysteine in ethanol and water System at 298.15 to 318.15 K at 5 K interval

Name of the system	Conc./ (w/v)%	ΔH* *KJ.mol^{-1}*	ΔS* *KJ.mol^{-1}*
Ethanol–NAC	1	13.6086	-0.0074
	5	13.5802	-0.0081
	10	13.7937	-0.0083
	15	13.7303	-0.0090
	18	13.7699	-0.0094
Water–NAC	1	15.9677	0.0043
	5	16.5196	0.0055
	10	17.2647	0.0072
	15	18.5405	0.0105
	18	19.0013	0.0114

Table 4.16: Change of Enthalpy, ΔH* and Entropy, ΔS* of NAC in [4:1], [3:2], [2:3], [1:4] ethanol–water System at 298.15 to 318.15 K at 5 K interval

Name of the system	Conc./ (w/v)%	ΔH* $KJ.mol^{-1}$	ΔS* $KJ.mol^{-1}$
[4:1] ethanol–water–NAC	1	19.8634	0.0136
	5	19.5796	0.0119
	10	19.9437	0.0122
	15	22.1054	0.0174
	18	21.9455	0.0161
[3:2] ethanol–water–NAC	1	17.2069	0.0033
	5	19.2848	0.0095
	10	18.8331	0.0073
	15	20.5651	0.0123
	18	19.5019	0.0082
[2:3] ethanol–water–NAC	1	18.0730	0.0043
	5	18.9180	0.0067
	10	19.8407	0.0091
	15	19.6120	0.0078
	18	20.9714	0.0119
[1:4] ethanol–water–NAC	1	19.8736	0.0097
	5	18.2462	0.0037
	10	18.7512	0.0048
	15	18.5516	0.0037
	18	18.9047	0.0045

CHAPTER V

Conclusion

Volumetric, viscometric and thermodynamic properties of N-Acetylcysteine were studied in ethanol, water and also in ethanol–water. NAC was found to be readily dissolved in ethanol, water and ethanol–water over a concentration range of 1-18 (w/v)%. Some interesting solution properties of these NAC in different systems were observed as follows:

(i) Volumetric, viscometric and thermodynamic properties are depended upon NAC concentration as well as on the temperature.

(ii) The apparent molar volume, φ_v values increased at all concentrations and temperatures.

(iii) The apparent molar volumes at infinite dilution φ_v^0 values of NAC in water, ethanol, ethanol–water mixtures are positive and provide worthy understanding between solute–solvent interaction.

(iv) Investigated systems showed small positive values for S_v which indicate that the solvation process involve strong interaction but not pure ionic.

(v) The viscosity values, η increased with concentration but decreased with temperature for all systems.

(vi) Viscosities, η were also found to be increased with increasing the ratio of water in ethanol.

(vii) The change of free energy, ΔG^* values for viscous flow are found to be positive for all the studied systems indicate that work has to be done to overcome the energy barrier for the flow process.

(viii) The positive ΔH values indicate that the viscous flow is not thermodynamically favored for the systems studied.

(ix) The ΔS^* values are positive for all the systems studied except ethanol–NAC system means that except ethanol–NAC system other binary and ternary systems are random that those of the pure one.

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