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VOLUMETRIC AND VISCOMETRIC STUDIES OF ENORMOUS MEDICINE N-ACETYL-L-CYSTEINE IN ETHANOL AND WATER

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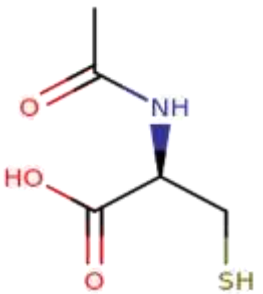
ABSTRACT: N-Acetyl-L-cysteine (NAC), the preacetylysed form of simple amino acid cysteine, a synthetic precursor of cysteine and reduced glutathione has been used in clinical widely as medicine. It is a powerful intracellular antioxidant, antitoxin improves immunity. NAC is a thiol compound which is also called acetylcysteine, is an amino acid with the molecular formula $C_5H_9NO_3S$. NAC converts into cysteine which is a nonessential amino acid produced by the human body. The unambiguous intentions of this study are comprehending interaction between Water+NAC and Ethanol+NAC and change of thermodynamic properties of NAC in water and ethanol. Volumetric and viscometric studies of binary mixtures of ethanol–NAC and water–NAC were done.

Density and viscosity of liquids is important physicochemical properties which affect mass and heat transfer of solutions. NAC had been investigated in binary system over a concentration range of (1-18) % (w/v) at 298.15 to 323.15 K at 5 K intervals. Apparent molar volumes,$\boldsymbol{\varphi_v}$, apparent molar volumes at infinite dilution ($\boldsymbol{\varphi_v^o}$), apparent molar expansivities are calculated by measuring density and thermodynamic properties are calculated from viscosity.



N-Acetyl-L-cysteine

KEYWORDS: N-Acetyl-L-cysteine (NAC), Ethanol, Water, Density, Apparent molar volumes, Apparent molar volumes at infinite dilution, Apparent molar expansivities, Viscosity, Enthalpy.

1. INTRODUCTION

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 [1]. Detoxifying properties of NAC were discovered in the 1970s and since then NAC was being used as an antidote in aminophenol intoxication [2]. Currently it is known mainly as an antioxidant displaying direct and indirect activities [3]. 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 [4] and cystic fibrosis. Increasing number of publications confirm efficacy of using NAC in the above mention diseases [3-7]. 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 [3]. 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 [7-8]. 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 [4]. Toxicological data shows that intakes of NAC per day orally could be consumed without causing significant adverse effects [9]. Most of anticancer therapies are based on growth of ROS production in cancer cells leading to their apoptosis [13-17]. Water is universal solvent used in daily life. Ethanol is the organic solvent also extensively used in various medicinal sectors. So investigation into interaction between NAC and water, NAC and ethanol or NAC could be quite interesting and applicable. The purpose of this study was to evaluate the miscibility of N-acetylcysteine in water and ethanol solution systems.

2. METHODS AND MATERIALS

2.1 Chemicals

N-acetylcysteine was collected from Sigma Aldrich, USA. High performance liquid chromatography (HPLC) graded 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.

2.2. METHODS

The densities of the solutions were determined by weighing a definite volume of the solution in a calibrated pycnometer (Glasgow, 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.

$$\rho = \frac{w - w_e}{v_0} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(1)$$

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

Viscosity of water, ethanol and several solutions were measured by using the Ostwald U-type viscometer are known (from literature) calibration constant A of the viscometer for different temperature were obtained by using equation,

$$\eta = A\rho t \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots (2)$$

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

$$\boldsymbol{\varphi_v} = \left[\frac{1000(\rho_0 - \rho)}{C\rho_0}\right] + \frac{M_2}{\rho_0} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

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 equation (4) and (5).

$$\varphi_v = \varphi_v^0 + S_v\sqrt{c} \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots \quad (4)$$

$$\varphi_v = \varphi_v^0 + S_v\sqrt{C} + b_v C \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots \quad (5)$$

Where $\boldsymbol{\varphi_v}$ is the apparent molar volume at infinite dilution and $\boldsymbol{b_v}$ is an experimentally determined parameter. 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 (6)

$$\varphi_E = \left(\frac{\delta\varphi_v}{\delta t}\right)_P \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (6)$$

Where $\varphi_E$the apparent molar expansivity, t is 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 expansivities at infinite dilution, φ_E^0, can be obtained if φ_v^0 values are used for $\varphi_v$in this treatment.

The values of change of free energy of activation (ΔG^*) can be calculated by using the Nightingle and Benck equation,

$$\Delta G^* = \mathrm{RT} \ln\left(\frac{\eta V}{hN}\right) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (7)$$

Values of enthalpy of activation, ΔH^*per mole for viscous flow of solutions have been calculated from the relationship

$$ln\frac{\eta V}{hN} = \frac{\Delta H^*}{RT} - \frac{\Delta S^*}{R} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (8)$$

3. Results and Discussion

The density values, ρ of NAC in ethanol and water were from 1 to 18 (w/v) % at 5 K intervals from 298.15 K to 318.15 K as mentioned in the Table -2 and Figure 1-2, while the experimented densities and viscosities of pure ethanol at mentioned temperatures have been shown in Table-1 together with the literature values, for possible comparison. From the results shown in Table-1 and 2 it can be stated that densities of ethanol solution of NAC are higher than those of the pure ethanol. This is may be due to the increase in density of 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 [18]. Water is a polar inorganic molecule which has 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 by establishing H–bonds. 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 are decreased than solvent, pure water. So the density of water-NAC is higher than ethanol -NAC as in Table-2. Apparent molar volume reveals the following characteristics: Solute–solvent interaction in the binary systems happened significantly. The addition of NAC in water and ethanol 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. The apparent molar volumes of infinite dilution φ_v^0 value of NAC in water, ethanol are calculated and tabulated in Table-3. Investigate systems showed small positive values of S_v in Table-3, which indicates that the solvation processes 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 of 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. 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. These values of molar expansivities at

infinite dilution (φ_E^0) are shown in Table-4. The expansivities values in 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 0.8008, quite acceptable. The values of viscosity, change of free energy are tabulated in Table-2. The values of viscosity (η) of NAC in ethanol and water increased with the increase of concentration and decrease considerably with temperature at a constant 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. The wide range of dissolution of NAC in water and ethanol might have intriguing aspects are consequence of the great ability of both water and alcohol to make hydrogen bonds. On the other hand NAC contains two polar groups –COOH and CH_3CONH–. It also contains almost nonpolar –SH group. Using this NAC makes strong interactions in water–NAC or ethanol–NAC binary 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 and water has been investigated at various temperatures and is shown in Figure 3-4. Thermodynamic properties, change of free energy, ΔG*, change of enthalpy, ΔH*, for viscous flow have been calculated from viscometric data. The ΔG*, values is positive about all the studied systems indicate that studied systems are non-spontaneous for the flow process as shown in Table-2 and it is spontaneous in the reverse direction. The positive free energy change, ΔG* for viscous flow may be interpreted by Furth model [19] 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 systems are more structured. Enthalpy is the thermodynamic quantity equivalent of the total heat content of a system. The change enthalpy, ΔH* values are positive for all the studied system as shown in Table-4. 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.

4. Conclusion

Volumetric, viscometric and thermodynamic properties are depended upon NAC concentration as well as on the temperature. The apparent molar volume, φ_v value increased at all concentrations and temperatures. The apparent molar volumes at infinite dilution φ_v^0 values of NAC in water and ethanol are positive and provide worthy understanding between solute–solvent interactions. Investigate systems showed small positive values for S_v which indicates that the solvation processes involve strong interaction but not pure ionic. The viscosity values, η increased with concentration but decreased with temperature for all the systems. 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. The positive ΔH values indicate that the viscous flow is not thermodynamically favored for the systems studied.

Table-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[20]	0.7894	1.0820[21]	1.0889
303.15	0.7813[20]	0.7850	0.9870[21]	0.9895
308.15	0.7761[20]	0.7804	0.9015[22]	0.9073
313.15	0.7718[20]	0.7765	0.8284[23]	0.8332
318.15	0.7651[20]	0.7723	0.7642[22]	0.7718

Table-2: Density, viscosity, apparent molar volume and gives free energy of NAC in Ethanol and Water at 298.15 to 318.15 K at 5 K interval.

		Ethanol–NAC				Water–NAC			
		ρ	η	φ_v	ΔG^*	ρ	η	φ_v	ΔG^*
298.15K	1	0.79567	1.13747	76.770	15.8123	0.99989	0.90962	116.31	14.6794
	5	0.81215	1.21787	112.61	15.9816	1.01081	0.98692	118.45	14.8816
	10	0.83468	1.36105	113.10	16.2571	1.02399	1.09216	119.50	15.1328
	15	0.85625	1.45519	114.59	16.4229	1.03705	1.23019	119.98	15.4278
	18	0.86381	1.54305	121.26	16.5682	1.04369	1.32741	121.23	15.6163
303.15 K	1	0.79122	1.03394	78.35	15.8510	0.99847	0.81366	116.79	14.6482
	5	0.80789	1.11364	112.66	16.0382	1.00887	0.87825	120.39	14.8407
	10	0.83049	1.23834	113.30	16.3045	1.02196	0.96537	120.70	15.0791
	15	0.85195	1.31270	115.09	16.4527	1.03429	1.07928	121.63	15.3602
	18	0.85961	1.40572	121.72	16.6252	1.04081	1.16563	122.74	15.5542
308.15K	1	0.78627	0.94018	86.12	15.8840	0.99669	0.73079	119.93	14.6187
	5	0.80334	1.01060	113.11	16.0690	1.00675	0.78744	122.29	14.8100
	10	0.82574	1.11891	114.29	16.3274	1.01912	0.86150	122.93	15.0402
	15	0.84752	1.19841	115.53	16.5057	1.03129	0.95641	123.36	15.3080
	18	0.85522	1.27984	122.19	16.6741	1.03802	1.02456	124.02	15.4844
313.15K	1	0.78230	0.85795	87.93	15.9165	0.99475	0.66439	122.35	14.6126
	5	0.79953	0.92500	113.31	16.1124	1.00495	0.70968	122.52	14.7843
	10	0.82166	1.03315	115.24	16.4002	1.01658	0.77534	124.36	15.0147
	15	0.84401	1.09360	115.56	16.5483	1.02772	0.85063	125.53	15.2560
	18	0.85133	1.16008	122.79	16.7019	1.03436	0.91006	125.95	15.4318
318.15K	1	0.7779	0.78937	92.00	15.9646	0.99262	0.60175	124.84	14.5893
	5	0.7947	0.84537	116.20	16.1459	1.00233	0.64497	124.82	14.7728
	10	0.8166	0.93614	117.56	16.4156	1.01405	0.69922	125.49	14.9864
	15	0.8386	1.00403	117.82	16.6008	1.02525	0.76353	126.30	15.2191
	18	0.8473	1.06820	123.17	16.7647	1.03068	0.81578	127.75	15.3942

Table-3: Apparent molar volume ($cm^3.mol^{-1}$), φ_v^0 at infinite dilution and Sv parameter of NAC in ethanol and water systems.

Temperature (K)	φ_v^0 ($cm^3.mol^{-1}$)		Sv	
	Ethanol–NAC	Water–NAC	Ethanol–NAC	Water–NAC
298.15	73.1168	115.0671	48.1183	5.6082
303.15	74.4706	115.6825	47.0106	6.6397
308.15	82.3045	119.1195	38.9196	4.7186
313.15	84.0712	120.6286	37.4573	4.8908
318.15	89.1555	123.5213	33.6976	3.2277

Table-4: `Apparent molar expansivities ($cm^3.mol^{-1}.K^{-1}$), φ_E^0 at infinite dilution and Change of Enthalpy, ΔH* of NAC in ethanol and systems.

Conc./ (w/v)%	φ_E^0 ($cm^3.mol^{-1}.K^{-1}$)		ΔH* *KJ.mol^{-1}*	
	Ethanol–NAC	Water–NAC	Ethanol–NAC	Water–NAC
1	0.8008	0.4524	13.6086	15.9677
5	0.1563	0.2971	13.5802	16.5196
10	0.2174	0.3129	13.7937	17.2647
15	0.1387	0.3307	13.7303	18.5405
18	0.0979	0.3250	13.7699	19.0013

Figure-1: Densities, ρ of N-Acetylcysteine in ethanol at 298.15 to 318.15 K at 5 K interval.

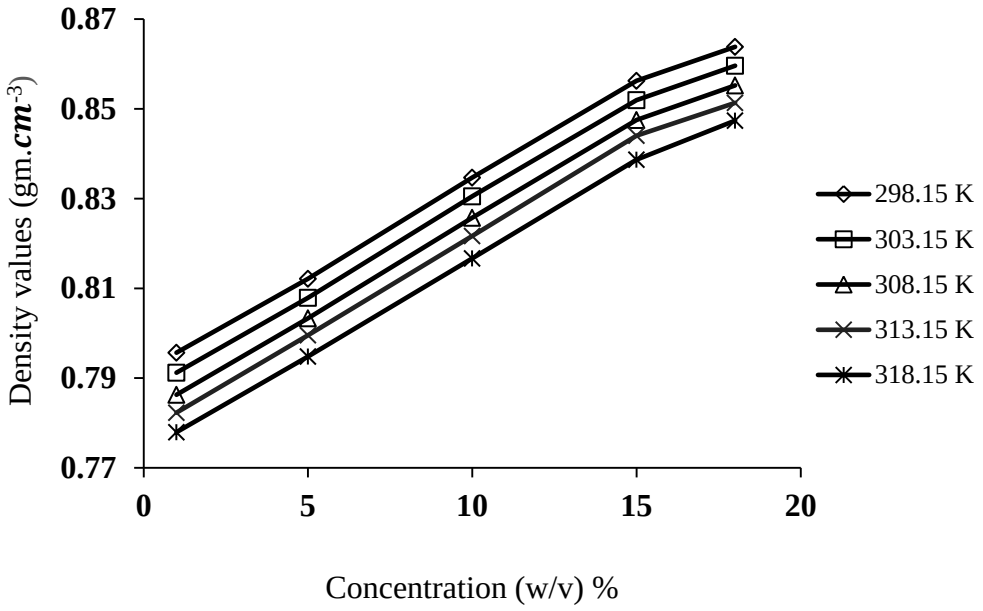


Figure-2: Densities, ρ of N- Acetylcysteine in water at 298.15 to 318.15 K at 5 K interval.

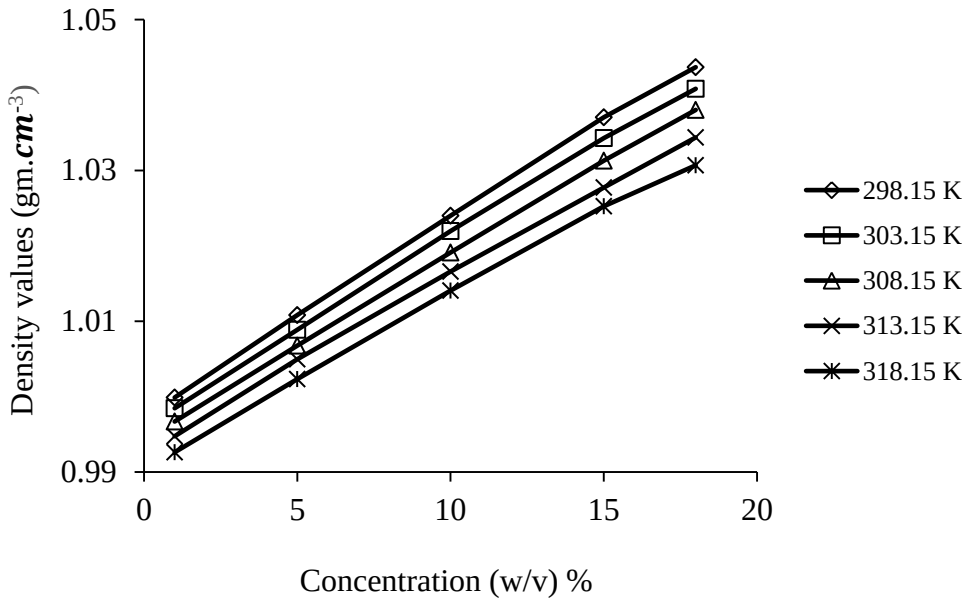


Figure-3: Viscosities (η), of N-Acetylcysteine in water at 298.15 to 318.15 K at 5 K interval.

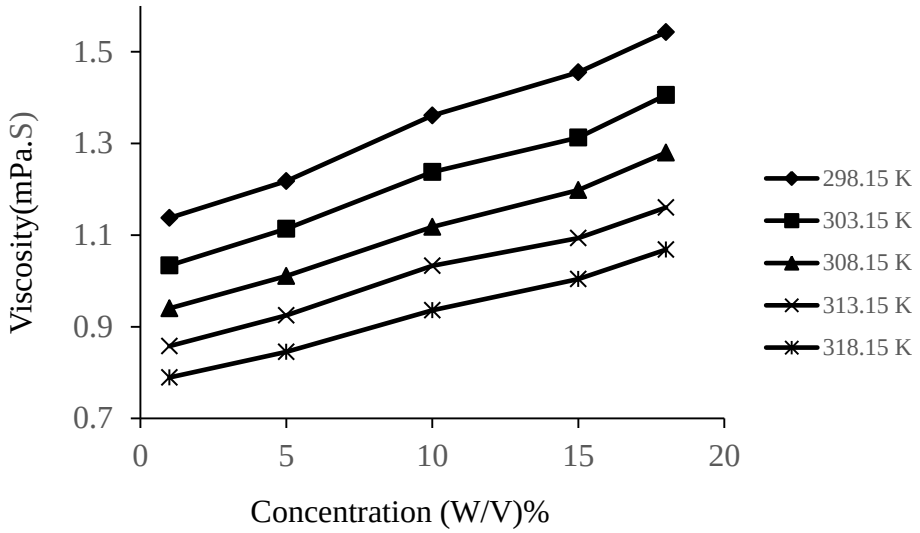
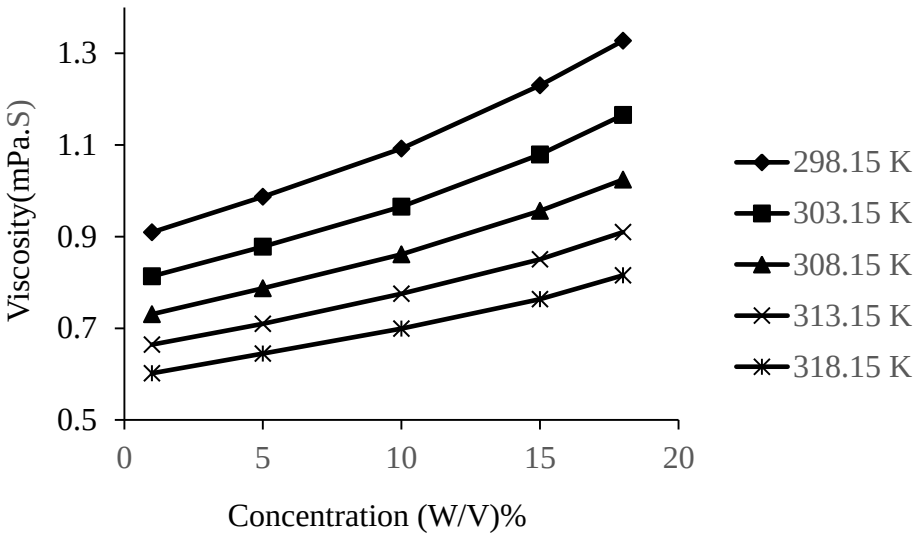


Figure-4: Viscosities (η), of N-Acetylcysteine in ethanol at 298.15 to 318.15 K at 5 K interval.



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