Volumetric and Acoustic Investigation of Citicoline Sodium in Aqueous Solutions over the Temperature Range (288.15-318.15) K

Rajshree P. Kolhe[1], Komal M. Jamkhande[1], Archana R. Chaudhari[2], Niraj T. Khaty[3], Vijay M. Tangde[1]*

[1]Department of Chemistry, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur 440033

[2] Department of Chemistry Nutan Adarsh Mahavidyalaya, Umred, Nagpur 440033

[3] Department of Chemistry, Laxminarayan Innovation Technological University, Nagpur 440033

*Email- vijaytn6@gmail.com

Received: 12.9.2026, Revised: 24.10.2026 Accepted: 25.10.2026

Abstract

The current study presents a methodical analysis of the volumetric and acoustic characteristics of Citicoline Sodium in aqueous solution at concentrations between (0.01-0.1) mol kg^{-1} and temperatures between (288.15-318.15) K at intervals of 5 K. Citicoline Sodium, an ionic pharmaceutical compound containing phosphate, hydroxyl, and quaternary ammonium functionalities, possesses several sites capable of interaction with water. The investigation was undertaken to characterize the thermophysical behavior of the Citicoline Sodium + Water binary system and to obtain information on its molecular interactions in aqueous media. The produced solutions' density and speed of sound were measured, and the experimental data were then utilized to assess apparent molal volume (V_ϕ), limiting apparent molar volume (V_ϕ^0), limiting apparent molar expansibilities (E_ϕ^0), isentropic compressibility (κ_S), apparent molal isentropic compressibility ($K_{s,\phi}$), limiting apparent molar isentropic compression of solute ($K_{S,\phi}^0$). According to reported results, Citicoline Sodium is a structure-breaking solute in aqueous solution, and temperature has a significant impact on its hydration behavior and molecular interactions. The negative ($K_{S,\phi}^0$) values suggest significant Citicoline Sodium + Water interactions and a less compressible solvation environment.

Keywords: Citicoline Sodium, Density, Speed of Sound, Apparent molal Volume, Apparent molal Isentropic Compressibility

1. INTRODUCTION

Citicoline is an endogenous nucleotide derivative that is involved in the synthesis of membrane phospholipids, especially phosphatidylcholine. It is sometimes referred to as cytidine 5′-diphosphocholine or CDP-choline[1]. Citicoline Sodium is the monosodium salt of Citicoline and is widely investigated as a pharmaceutical compound because of its relevance to neurological and cerebrovascular disorders. Chemically, citicoline sodium contains a cytidine moiety linked through a diphosphate group to a trimethylammonium-containing choline residue. Citicoline Sodium has the chemical formula $C_{14}H_{25}N_4NaO_{11}P_2$ and a molar mass of 510.31 (g/mol)[2]. Citicoline is an important intermediate in phosphatidylcholine metabolism and has been investigated for its potential neuroprotective effects. Previous biochemical studies have suggested that its biological action may be associated with preservation and restoration of membrane phospholipids, attenuation of lipid peroxidation, and modulation of cellular energy and membrane-related processes[3]. Phosphate groups, hydroxyl groups, amino functionality, and a permanently charged quaternary ammonium group are among the hydrophilic functional groups found in the chemical structure of Citicoline Sodium. As a result, a mix of ion-dipole interactions, hydrogen bonding, electrostatic interactions, and rearrangement of the surrounding solvent molecules is anticipated in its interaction with water[4] .

Citicoline Sodium is an important nucleotide-derived compound with applications in pharmaceutical, nutraceutical, ophthalmic, and pharmaceutical-process research. In the pharmaceutical field, Citicoline is used as an active ingredient in formulations associated with neurological and cerebrovascular applications, while its biological relevance is related to its role as a source of choline and cytidine following hydrolysis[3]. Citicoline has also been investigated in ophthalmology, particularly as an adjunctive neuroprotective agent in glaucoma and other optic-neural disorders[5]. Beyond therapeutic applications, Citicoline is used as an ingredient in food and nutritional supplements and has been evaluated for safety as a novel food ingredient[6]. The crystallisation behaviour of Citicoline Sodium is of great relevance in pharmaceutical processing because crystal agglomeration, particle size distribution, crystal habit, nucleation, and induction time can all have an impact on material processing. Consequently, ultrasound-assisted antisolvent crystallisation has been explored as an approach to modulating the crystallisation attributes of Citicoline Sodium[7]. These diverse applications illustrate the vital importance of understanding the physicochemical behaviour of Citicoline Sodium in aqueous environments.

.

From a physicochemical perspective, both solute-solvent and solute-solute interactions have a substantial impact on how a pharmaceutical molecule behaves in water. Water is the primary medium in biological systems and is frequently employed in pharmaceutical formulation and processing, indicating that these interactions are of crucial importance[8]. Volumetric and acoustic measurements effectively study molecular interactions in solution. Density measurements reveal the apparent molal volume of solutes, providing insights into their volume and the solvent's structural changes[7,9].

The slope for solute–solute interactions and the limiting apparent molal volume for solute–solvent interactions are important factors[10]. Additionally, the speed of sound measurements in solutions inform about compressibility and structural properties through the Newton–Laplace relationship, leading to insights on hydration and compression effects[11]. Temperature significantly influences molecular interactions, impacting hydrogen bonding, hydration, and solvent structure, thus necessitating investigations across a range of temperatures for comprehensive analysis[12].

Consequently, information about hydration, solvation, molecular packing, and structural changes taking place in the solvent environment around the solute can be obtained by understanding the thermophysical characteristics of drug-water systems. In this regard, in the current work, an experimental investigation of the density and speed of sound in the binary aqueous system of Citicoline Sodium has been carried out at intervals of 5 K over the temperature range of (288.15-318.15) K. The volumetric and acoustic characteristics of Citicoline Sodium in aqueous solution, including apparent molar volume ($V_{\emptyset}$) and apparent molal isentropic compressibility ($K_{s,\emptyset}$) parameters were then assessed using the experimental data. The temperature dependence of these properties was examined in order to get further insight into the interactions of Citicoline Sodium in an aqueous medium and the structural characteristics of the ensuing aqueous solutions. Thus, the goal of the current study is to give a methodical thermophysical description of Citicoline Sodium in aqueous media and to provide quantitative information that will help comprehend its molecular solvation behavior.

.

2. MATERIALS AND METHODS

2.1. Materials

The pharmaceutical solute under investigation was Citicoline Sodium (CAS No. 33818-15-4). With a purity of (≥ 98.60%), the Citicoline Sodium sample was acquired from [Cadchem, Punjab, India] and utilised without additional purification. All aqueous solutions were prepared using double-distilled/deionised water having a conductivity less than 1×10^{-6} μS·cm^{-1} obtained from Evoqua water purifying system. The water used in the experiment was newly produced.

2.2. Methods

An Anton Paar DSA 5000 density and speed of sound analyzer was used to determine the density and speed of sound of the aqueous Citicoline Sodium solutions. The DSA method uses an ultrasonic method to detect speed of sound and a vibrating-tube approach to measure density. The current measurements were conducted at atmospheric pressure across the following temperature ranges: (288.15 - 318.15) K.

3. RESULT AND DISCUSSION

3.1 Volumetric properties

3.1.1. Density

Table 1 displays the experimental density data for the binary Citicoline Sodium + Water system at temperatures between 288.15K and 318.15K. The device was calibrated using doubly distilled deionised water at the experimental temperature range of (288.15−318.15) K prior to measuring the density of aqueous drug solutions. By comparing the published data of densities of diluted aqueous NaCl solutions over the temperature range of (288.15−318.15) K, the uncertainties in the experimental results of density values were ascertained[13]. The determined experimental standard uncertainties for density values were 0.05 kg.m^{-3}. The measured density consistently increases as the molality of Citicoline Sodium rises, contradicting a contrary temperature connection. At a fixed concentration, the density gradually decreases when the temperature is raised from (288.15- 318.15) K. The addition of Citicoline Sodium to the aqueous medium and the resulting alteration of the solution's molecular packing are the main causes of the density rise with concentration[14]. The elevated density suggests that the solute's mass is accompanied by a relatively lesser rise in effective solution volume. Significant solute–solvent interactions and

.

ionic/polar group hydration are consistent with this behavior. Specifically, the local arrangement of water molecules surrounding the solute can be altered by ion-dipole interactions between the charged groups of Citicoline Sodium and Water molecules. Because molecular packing and hydration also contribute to the volumetric response, the observed density increase should not be completely attributed to the molecular mass of Citicoline Sodium. The dependence on temperature is likewise systematic. The solution expands and the density decreases as the temperature rises because it increases the average intermolecular spacing and molecular translational motion. The observed decline could also be attributed to temperature-induced reorganization of the hydration environment. The current behavior is in good agreement with volumetric investigations of pharmaceutical and aqueous electrolyte systems that have been reported. For instance, studies on creatinine hydrochloride solutions using an Anton Paar DSA 5000 M revealed that density decreased with rising temperature and increased linearly with solute concentration[15]. For sodium salicylate, another ionic medicinal substance, similar density and acoustic measurements have also been documented; the volumetric characteristics were explained in terms of solute-solvent and solute-solute interactions[16].

Table 1. Molality (m) and Density (ρ) data for Citicoline Sodium in aqueous solutions at T = (288.15 - 318.15) K.

m	ρ / kg.m^{-3}						
/mol.kg^{-1}	288.15 K	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K	318.15 K
Citicoline Sodium + Water							
0.00000	999.13	998.21	997.08	995.69	994.08	992.27	990.27
0.01011	1001.04	1000.12	998.98	997.58	995.97	994.16	992.16
0.02016	1002.92	1001.99	1000.85	999.44	997.83	996.01	994.00
0.02995	1004.73	1003.79	1002.64	1001.23	999.61	997.79	995.78
0.04009	1006.58	1005.63	1004.48	1003.07	1001.44	999.62	997.61
0.05035	1008.43	1007.47	1006.32	1004.91	1003.27	1001.44	999.43
0.06042	1010.22	1009.27	1008.11	1006.69	1005.05	1003.22	1001.20
0.07031	1011.97	1011.00	1009.85	1008.42	1006.78	1004.93	1002.91
0.08029	1013.71	1012.74	1011.57	1010.15	1008.50	1006.65	1004.63
0.09042	1015.46	1014.48	1013.32	1011.88	1010.23	1008.38	1006.34
0.10051	1017.17	1016.19	1015.03	1013.60	1011.94	1010.07	1008.03

.

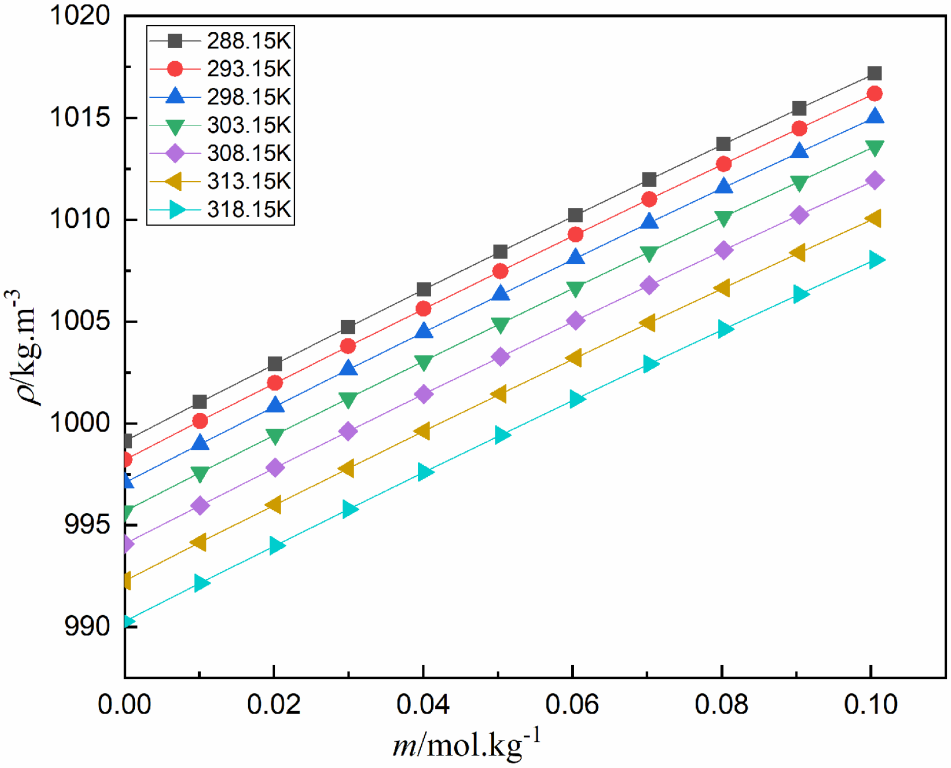


Fig 1. Variation of density (ρ) data function of molality (m) of Citicoline Sodium in aqueous solutions at T = (288.15 - 318.15) K.

3.1.2 Apparent Molal Volume

A helpful indicator of the solute's volumetric contribution to the solution, the apparent molal volume $V_{\emptyset}$ is especially relevant for analysing solute-solvent interactions. The following equation is used to evaluate it:

$$V_{\emptyset} = \left(\frac{M}{\rho}\right) - \left(\frac{(\rho-\rho_0)}{m\rho\rho_0}\right) \quad (1)$$

The values obtained for Citicoline Sodium + Water are given in Table 2. A clear and systematic increase in $V_{\emptyset}$ is observed with increasing Citicoline Sodium concentration at every investigated temperature. The concentration dependence is highly linear. The effective molar volume linked to Citicoline Sodium appears to be increasing as the solute concentration rises, according to the

.

positive concentration dependency of $V_{\emptyset}$. Citicoline Sodium + Water interactions dominate the aqueous environment at low concentrations. The average distance between solute species decreases with increasing concentration, making solute-solute interactions more significant. Thus, solute-solvent hydration, solute-solute interactions, and alterations in the structure of the surrounding water all contribute to the resulting apparent molal volume. The temperature dependence is particularly noteworthy. $V_{\emptyset}$ Increases systematically with temperature at all concentrations. The increase is consistent with thermal expansion of the solute's partial-volume contribution and temperature-dependent rearrangement of the hydration environment. An increase in $V_{\emptyset}$ with temperature does not, by itself, establish that hydration becomes stronger or weaker. The apparent volume is the net result of several competing effects. Increasing temperature can reduce the extent of electrostrictive contraction around charged groups while simultaneously increasing the intrinsic volume of the hydrated solute environment through thermal expansion. The measured positive temperature dependence therefore indicates a net expansion of the effective solute environment. Comparable behavior has been reported in volumetric investigations of aqueous electrolyte systems. Dunn's classical study of aqueous electrolytes showed that apparent molar volumes possess pronounced temperature dependence and that their concentration dependence changes with temperature[17]. $V_{\emptyset}$ is also used as a sensitive metric in more recent studies of pharmaceutical/electrolyte systems to resolve alterations in solute-solvent and solute-solute interactions[18].

Table 2. Molality (m) and Apparent molal volume ($V_{\emptyset}$) data for Citicoline Sodium in aqueous solutions at T = (288.15 - 318.15) K.

m /mol.kg^{-1}	10^6. $\boldsymbol{V}_{\emptyset}$ / m^3.mol^{-1}						
	288.15 K	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K	318.15 K
Citicoline Sodium + Water							
0.00000	320.4	321.3	321.9	322.6	323.2	323.8	324.3
0.01011	320.8	321.7	322.4	323.0	323.7	324.2	324.7
0.02016	321.2	322.0	322.7	323.4	324.0	324.6	325.2
0.02995	321.7	322.5	323.0	323.7	324.4	325.1	325.6
0.04009	322.1	322.9	323.5	324.2	324.8	325.4	326.0

.

0.05035	322.5	323.3	323.9	324.5	325.2	325.9	326.5
0.06042	322.9	323.7	324.3	324.9	325.6	326.3	326.9
0.07031	323.3	324.1	324.6	325.2	326.0	326.8	327.4
0.08029	323.7	324.5	325.1	325.6	326.4	327.2	327.8
0.09042	324.1	324.9	325.4	326.1	326.8	327.5	328.3
0.10051	324.6	325.3	325.8	326.4	327.2	328.0	328.7

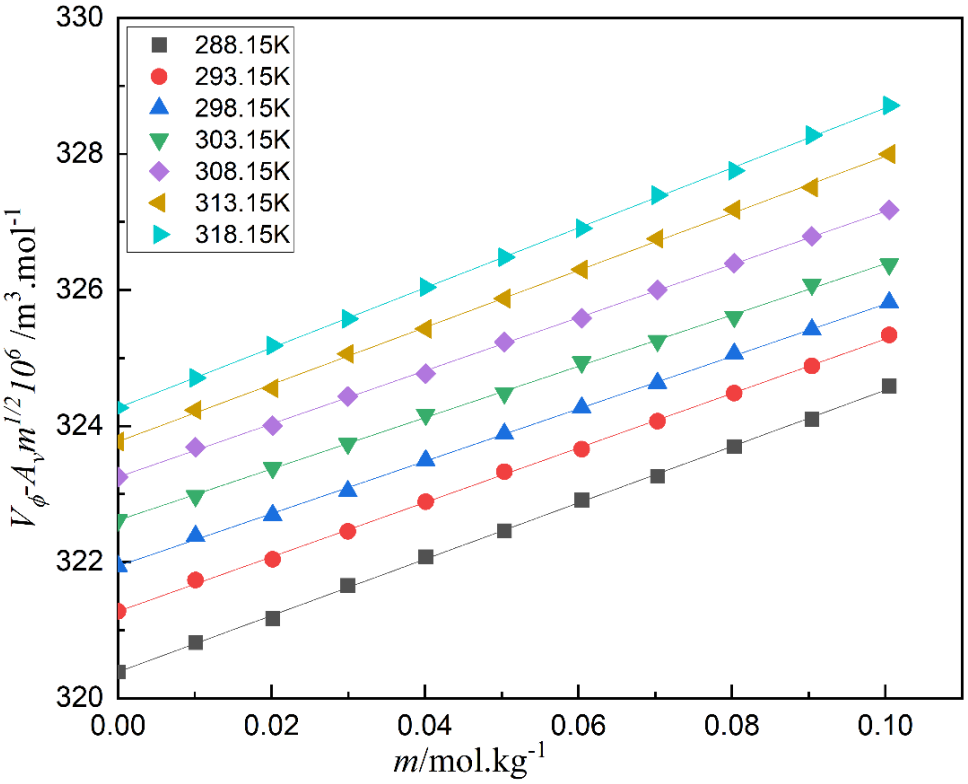


Fig 2. Variation of apparent molal volume (V_ϕ) and molality (m) data of citicoline sodium in aqueous solutions at T = (288.15-318.15) K.

.

3.1.3 Limiting Apparent molar volume

The limiting apparent molar volume ($V_\emptyset^0$), represents the apparent volume contribution of one mole of solute at infinite dilution. At this condition, solute–solute interactions become negligible, and therefore ($V_\emptyset^0$), is particularly useful for assessing the interaction of an isolated solute species with the surrounding solvent. It can be regarded as being closely related to the partial molar volume of the solute at infinite dilution. Consequently, its magnitude contains contributions from the intrinsic volume of the solute as well as volume changes produced in the solvent through electrostatic interactions, hydration, hydrogen bonding and structural rearrangement.

Since, Citicoline Sodium behaves as an electrolyte in aqueous medium, the limiting Debye–Hückel equation for apparent molar volume was employed to determine the limiting apparent molar volume ($V_\emptyset^0$) and reported in table 5,

$$V_\emptyset = V_\emptyset^0 + A_v\sqrt{m} + S_v m. \quad (2)$$

For Citicoline Sodium, $V_\emptyset^0$ is positive throughout the investigated temperature range and increases progressively. The continuous increase of $V_\emptyset^0$ with temperature indicates that the effective volume associated with the hydrated solute increases on heating. Such behavior can be attributed to progressive modification of the hydration environment, particularly weakening or partial release of solvent molecules from the more tightly associated solvation region into the bulk phase. The progressive increase with temperature is therefore more appropriately viewed as evidence for a temperature-dependent alteration of the hydration structure rather than simply an increase in the strength of solute–solvent association.

Further, limiting slope (S_v), reported in table 5, is the concentration-dependent interaction parameter obtained from the limiting volume relationship. Unlike $V_\emptyset^0$, which primarily reflects solute–solvent interactions at infinite dilution, S_v provides information about solute–solute interactions as the solute concentration increases. The positive sign throughout the temperature range indicates that interactions between Citicoline Sodium species are significant in the investigated concentration region. The non-monotonic temperature dependence suggests that these interactions are sensitive to the changing organization of the aqueous medium. The decrease in S_v up to 303.15K may indicate a reduction in the effective solute–solute contribution as the hydration environment becomes thermally modified, whereas the subsequent increase

.

suggests that the balance between solute association and solvent restructuring changes again at higher temperatures. Importantly, the consistently positive S_v values are compatible with the hydrophilic character of Citicoline Sodium, although the temperature-dependent variation indicates that the extent of these interactions is not constant.

3.1.4 Limiting Apparent Molar Expansibilities

The limiting apparent molar expansibility, ($E_\emptyset^0$), is defined as the temperature derivative of the limiting apparent molar volume and describes how the limiting volume contribution of the solute responds to temperature. It is calculated by following expression, and is reported in table 5,

$$E_\emptyset^0 = (\frac{\partial V_\emptyset^0}{\partial T}) \quad (3)$$

It is therefore particularly valuable for examining the thermal response of the solvation environment. In aqueous electrolyte solutions, $E_\emptyset^0$ contains contributions associated with changes in electrostriction and structural rearrangement of the solvent.

The $E_\emptyset^0$ values obtained for Citicoline Sodium are positive over the entire investigated temperature range, which indicate that the effective volume surrounding Citicoline Sodium responds positively to heating, consistent with a hydrated solute whose surrounding water structure undergoes thermal expansion and rearrangement. The positive sign is also consistent with the predominance of solute–solvent effects over purely solute–solute contributions in determining the thermal volume response.

Hepler's constant[19] is obtained from the temperature dependence of $E_\emptyset^0$ and provides a qualitative criterion for the effect of a solute on the structure of the solvent. It is evaluated with following equation, and is reported in table 5,

$$\frac{(\partial E_\emptyset^0}{\partial T}) = \frac{(\partial^2 V_\emptyset^0}{\partial T^2)} \quad (4)$$

Hepler[19] claims that a good way to determine whether the solute functions as a structure constructor or breaker in the solution is to look at the sign of the second derivative of $V_\emptyset^0$ i.e. It was suggested that a structure constructor would be shown by positive values, and a structure

.

breaker by negative values. For Citicoline Sodium, the reported Hepler's constant values are negative, thus Citicoline Sodium acts as a structure breaker.

3.2. Acoustic properties

3.2.1 Speed of Sound

Table 3 contains a list of the experimental speed of sound data. The device was calibrated using doubly distilled deionised water at the experimental temperature range of (288.15−318.15) K prior to measuring the speed of sound of aqueous medication solutions. By comparing the literature data on the speed of sound of pure water over the temperature range of (288.15−318.15) K, the uncertainties in the experimental results of speed of sound values were ascertained[13]. The experimental standard uncertainties for speed of sound values were 0.5 $m \cdot s^{-1}$. A pronounced increase in ultrasonic velocity is observed with both Citicoline Sodium concentration and temperature. The concentration-induced increase in speed of sound indicates that incorporation of Citicoline Sodium modifies the compressibility and molecular organization of the aqueous medium. Since ultrasonic propagation is directly influenced by the elastic response of a liquid, the increase in *u* can be associated with changes in intermolecular cohesion and the organization of water around the ionic/polar portions of the solute. The concentration effect becomes progressively smaller at higher temperature, suggests that thermal agitation partially reduces the concentration-induced modification of the acoustic environment. The simultaneous rise in temperature-dependent speed of sound and density-normalized acoustic response suggests that both structural and thermal factors influence the system's acoustic behavior. Similar density, speed of sound methodologies has been extensively employed for aqueous pharmaceutical and electrolyte systems. In order to determine apparent molar volume and compressibility, related parameters as well as to understand molecular interactions in aqueous media, studies of sodium salicylate and creatinine hydrochloride have employed simultaneous density and speed of sound measurements[10].

.

Table 3. Molality (m) and Speed of sound (u) data for Citicoline Sodium in aqueous solutions at T = (288.15 - 318.15) K.

m	u / m.s^{-1}						
/mol.kg^{-1}	288.1 K	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K	318.15 K
Citicoline Sodium + Water							
0.00000	1465.7	1482.2	1496.9	1509.5	1520.2	1529.1	1536.7
0.01011	1467.9	1484.4	1499.0	1511.5	1522.0	1530.8	1538.4
0.02016	1470.1	1486.4	1501.0	1513.4	1523.7	1532.5	1540.0
0.02995	1472.2	1488.4	1502.9	1515.3	1525.4	1534.1	1541.5
0.04009	1474.3	1490.5	1504.9	1517.1	1527.1	1535.7	1543.1
0.05035	1476.5	1492.6	1506.8	1518.9	1528.8	1537.4	1544.6
0.06042	1478.6	1494.6	1508.7	1520.7	1530.5	1539.0	1546.2
0.07031	1480.6	1496.6	1510.5	1522.4	1532.1	1540.5	1547.6
0.08029	1482.7	1498.5	1512.3	1524.0	1533.7	1542.1	1549.1
0.09042	1484.7	1500.5	1514.1	1525.6	1535.3	1543.6	1550.6
0.10051	1486.8	1502.5	1516.0	1527.3	1536.9	1545.3	1552.0

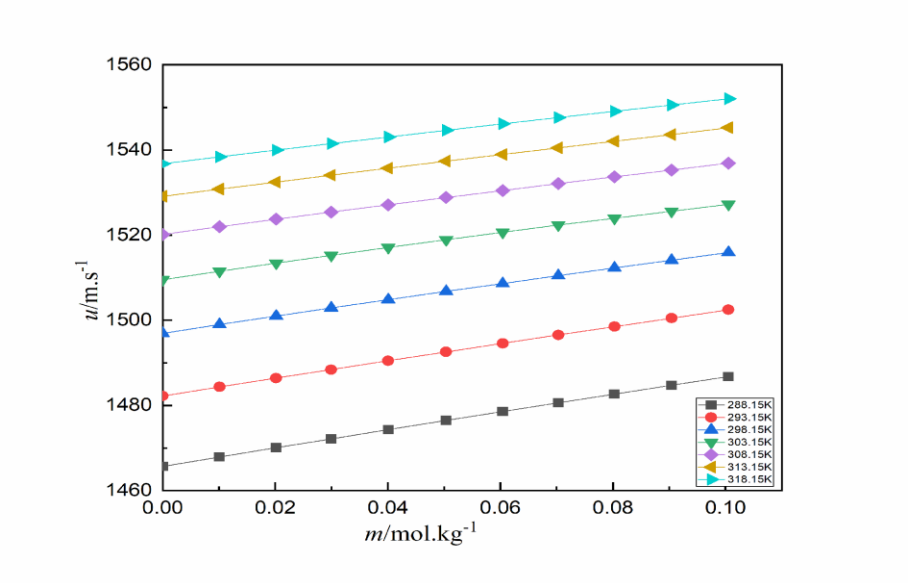


Fig.3. Variation of speed of sound (u) as a function of molality (m) of citicoline sodium in aqueous solutions at T = (288.15-318.15) K.

.

3.2.2 Apparent Molar Isentropic Compressibility

Further details on the solute's compressibility response in the solution can be found in the apparent molar isentropic compressibility, $K_{s,\emptyset}$. The apparent molar isentropic compressibility has been calculated using the following formula,

$$K_{s,\emptyset} = \left[\frac{(\rho_0\kappa_s - \rho\kappa_{s0})}{m\rho\rho_0}\right] + \left[\frac{M\kappa_s}{\rho}\right] \quad (5)$$

Table 4 reports the values of $K_{s,\emptyset}$. Table 4's key finding is that, as concentration and temperature rise, $K_{s,\emptyset}$ become less negative. The negative values can be interpreted as evidence that the introduction of Citicoline Sodium produces a less compressible effective solute environment relative to the reference solvent contribution. Ionic and polar groups can organize neighboring water molecules into locally constrained hydration environments. Such ion-water interactions can generate regions that respond differently to pressure compared with bulk water. The progressive movement toward less negative values with concentration indicates that the compressibility response changes as the solute concentration increases. This can arise from increasing solute–solute proximity and modification/overlap of hydration environments. Consequently, the observed concentration dependence should be regarded as the combined consequence of ion-water interactions and changing solute-solute contributions, rather than being assigned exclusively to hydration. This movement toward zero with increasing temperature is consistent with increasing molecular mobility and temperature-induced reorganization of the hydration environment. Similar acoustic research has explained apparent molar isentropic compressibility in terms of solvent molecule structure changes and hydrophilic/ionic interactions. For example, work on creatinine hydrochloride explicitly relates concentration-dependent volumetric and compressibility properties to hydrophilic-ionic and hydrophilic-hydrophilic interactions[20]. Studies of other aqueous ionic systems have similarly demonstrated that temperature can substantially alter electrostriction and hydration behavior[21]. Thus, the reported finding suggests strong attractive interactions between the dissolved solute and solvent molecule.

.

3.2.3 Limiting Apparent Molar Isentropic Compressibility of Solute

The limiting apparent molar isentropic compressibility ($K_{S,\emptyset}^{0}$), was obtained by extrapolating ($K_{s,\emptyset}$) against $m^{(1/2)}$ to zero concentration and it is calculated by following equation and is reported in table 5,

$$K_{S,\emptyset} = K_{S,\emptyset}^{0} + S_k(m)^{1/2} \quad (6)$$

The limiting value provides information on the solute–solvent interactions under infinite-dilution conditions, whereas the corresponding experimental slope (S_k) reflects the concentration-dependent contribution associated with solute–solute interactions. The ($K_{S,\emptyset}^{0}$), values obtained for Citicoline Sodium are negative over the entire investigated temperature range and ($K_{S,\emptyset}^{0}$) becomes progressively less negative with increasing temperature. The negative values indicate that the solvent molecules in the vicinity of Citicoline Sodium are less compressible than the bulk solvent, which is consistent with significant attractive solute–solvent interactions and the formation of a relatively compact solvation environment. The gradual movement of ($K_{S,\emptyset}^{0}$) toward less-negative values with increasing temperature indicates a weakening of this compression-resistant solvation environment. Thermal agitation increases molecular disorder and modifies the organization of water molecules surrounding the solute, thereby reducing the extent to which the hydration region resists compression. Consequently, although the negative sign is retained throughout the investigated temperature interval, the magnitude of ($K_{S,\emptyset}^{0}$) shows that the solvation structure becomes progressively less rigid on heating.

The experimental limiting slope (S_k), is reported in table 5, obtained from the dependence of ($K_{S,\emptyset}^{0}$) on $m^{(1/2)}$, is used to assess the concentration-dependent contribution of solute–solute interactions. Positive S_K values indicate that solute–solute interactions are relatively insignificant compared with solute–solvent interactions. In all investigated systems, these values are positive at all temperatures, suggesting minimal solute-solute interactions relative to solute-solvent interactions.

.

Table 4. The binary system's molality (m) and apparent molar isentropic compressibility ($K_{s,\emptyset}$) at T = (288.15-318.15) K.

m /mol.kg^{-1}	10^{15}. $K^0_{s,\emptyset}$ / m^3. Pa^{-1}. mol^{-1}						
	288.15 K	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K	318.15 K
Citicoline Sodium + Water							
0.00000	-85.9	-74.4	-70.4	-66.7	-51.7	-42.8	-39.4
0.01011	-79.5	-69.1	-63.5	-58.0	-45.6	-37.9	-34.1
0.02016	-77.1	-67.1	-60.3	-54.5	-43.1	-36.0	-32.0
0.02995	-75.2	-65.4	-58.3	-52.0	-41.4	-35.0	-30.7
0.04009	-74.0	-64.5	-56.6	-49.9	-39.7	-33.8	-29.3
0.05035	-72.6	-63.2	-55.4	-48.0	-38.4	-32.8	-28.3
0.06042	-71.2	-62.2	-53.4	-46.3	-37.1	-31.6	-27.2
0.07031	-70.0	-61.1	-52.1	-44.7	-36.0	-30.5	-25.9
0.08029	-68.6	-60.0	-50.7	-42.7	-34.6	-29.5	-24.9
0.09042	-67.4	-58.9	-49.5	-40.8	-33.6	-28.6	-23.9
0.10051	-66.3	-57.9	-48.4	-39.5	-32.5	-28.1	-22.9

Table 5. Limiting values of apparent molar volume ($V^0_\emptyset$), apparent molar compression ($K^0_{s,\emptyset}$) and apparent molar expansibility ($E^0_\emptyset$), their corresponding limiting slopes (S_V) and (S_K), Hepler's constant $\left(\frac{\partial^2 V^0_\emptyset}{\partial T^2}\right)$ data for Citicoline Sodium in aqueous solutions at T = (288.15-318.15) K.

T/K	$10^6.\boldsymbol{V^0_\emptyset}$ / m^3.mol^{-1}	10^6 .S_V / m^3.mol^{-2}.kg	$10^{15}.\boldsymbol{K^0_{s,\emptyset}}$/ m^3.Pa^{-1}.mol^{-1}	$10^{14}.S_K$ / m^3.Pa^{-1}.mol^{-2}.kg	$10^6.\boldsymbol{E^0_\emptyset}$ / m^3.mol^{-1}.K^{-1}	$10^6 \cdot\left(\frac{\partial^2 V^0_\emptyset}{\partial T^2}\right)$ m^3.mol^{-1}. K^{-2}
Citicoline Sodium + Water						
288.15	320.4	45.4	-85.9	6.1		
293.15	321.3	44.0	-74.4	5.1	0.133	
298.15	321.9	42.4	-70.4	6.9	0.135	
303.15	322.6	41.6	-66.7	8.5	0.127	-0.003
308.15	323.3	43.0	-51.7	6.0	0.104	

.

313.15	323.8	45.9	-42.8	4.6	0.099
318.15	324.3	48.0	-39.4	5.1	

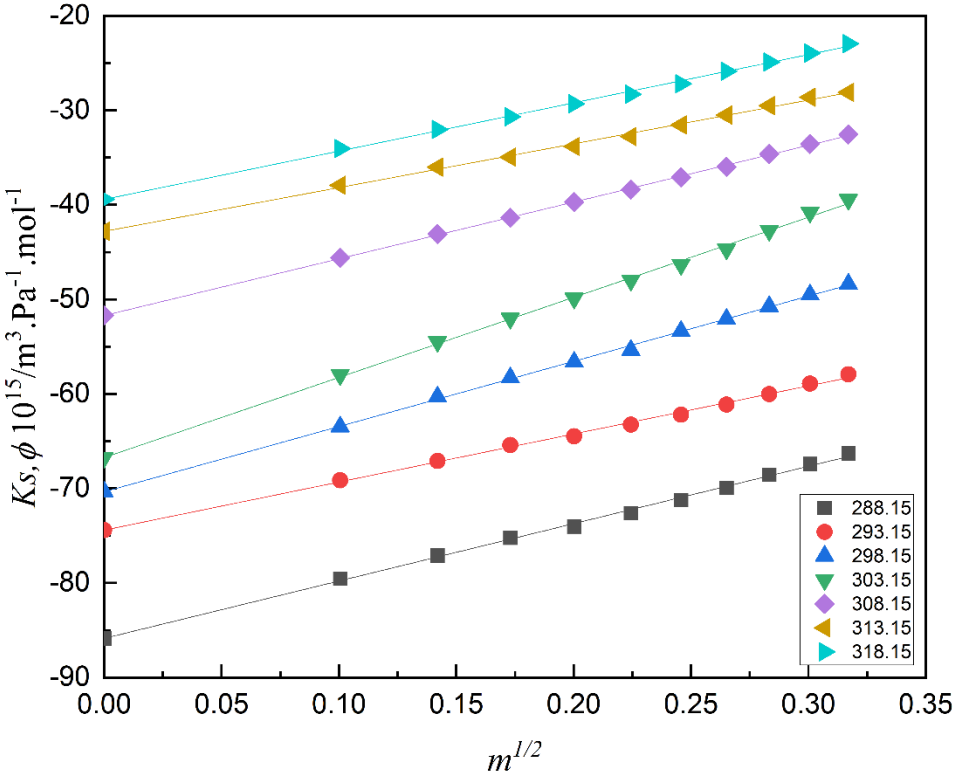


Fig. 4. Variation of apparent molar isentropic compressibility ($K_{s,\emptyset}$) as a function of molality ($m^{1/2}$) of Citicoline Sodium in aqueous solutions at T = (288.15-318.15) K.

4. CONCLUSION

Taken together, the results indicate that Citicoline Sodium significantly perturbs the local structure of water. It is anticipated that interactions between the ionic/polar groups of Citicoline Sodium and nearby water molecules will be the main source of contribution at lower concentrations. With increasing concentration, the hydration regions associated with neighboring solute molecules become increasingly important, allowing solute-solute interactions and overlap

.

of hydration environments to contribute to the observed volumetric and acoustic response. The increase in $V_{\emptyset}$ with temperature, combined with the reduction in the magnitude of negative $K_{s,\emptyset}$, suggests that thermal effects progressively modify the compactness and compressibility of the solvation environment. Therefore, the concentration and temperature effects should be considered together rather than independently when describing the molecular behavior of the Citicoline Sodium + Water system. The presence of significant solute-solvent interactions in aqueous Citicoline Sodium is supported by the collective experimental data. The molecule's ionic nature offers advantageous locations for interaction with water, and its numerous polar groups can take part in ion-dipole and hydrogen-bonding interactions. These interactions alter the local organization of water and consequently influence density, speed of sound. At higher concentrations, the increasing contribution of solute-solute interactions must also be considered. There is no discernible abrupt structural transition inside the experimental domain, according to the excellent linearity of the density, apparent molar volume, speed of sound and apparent molar isentropic compressibility data within the investigated concentration range. Instead, the system exhibits a gradual modification of its molecular environment. The observed trends therefore support a model in which hydration and ionic solute–water interactions dominate the low-concentration behavior, while increasing solute concentration progressively introduces a greater contribution from solute–solute interactions and overlapping hydration environments.

Overall, the volumetric and expansivity parameters indicate that Citicoline Sodium exhibits significant interactions with the aqueous medium, accompanied by appreciable solute–solute interactions and a temperature-dependent modification of its hydration environment. The positive $V_{\emptyset}^{0}$, S_{v} and $E_{\emptyset}^{0}$ values reflect favorable interactions and thermal expansion of the solvation environment, whereas the negative Hepler's constant confirms the tendency of Citicoline Sodium to disrupt the structural organization of water. Thus, Citicoline Sodium can be characterized as a structure-breaking solute in aqueous solution, with its molecular interactions and hydration behavior being strongly influenced by temperature. The isentropic compression results show that Citicoline Sodium has a considerable influence on the compressibility of the surrounding aqueous medium. $K_{s,\emptyset}^{0}$ values are typically negative, indicating strong solute-solvent interactions and a less compressible solvation environment. Thermal impacts decrease the solvent structure, as seen by the consistent shift in $K_{s,\emptyset}^{0}$ toward less-negative values as

.

temperature increases. Thus, the isentropic compression study supports strong Citicoline Sodium + Water interactions while also indicating a temperature-induced decrease in the stiffness of the related solvation structure.

Author's Contribution

Rajshree P. Kolhe: Data curation, Writing – original draft. **Komal M. Jamkhande**: Data curation. **Archana R. Chaudhari:** Data curation, Supervision, **Niraj T. Khaty**: Validation, Visualization, Investigation. **Vijay M. Tangde**: Investigation, Data curation, Validation.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

V.M.T. sincerely acknowledge the financial support received from the Rajiv Gandhi Science and Technology Commission (RGSTC), Government of Maharashtra, India.
K.M.J. is thankful to the Mahatma Jyotiba Phule Research and Training Institute for awarding the Mahatma Jyotiba Phule Research Fellowship–2022 (MJRF-2022), under reference number MAHAJYOTI/2022/Ph.D. Fellow/1002 (424), Government of Maharashtra, India.

References

1. J. J. Secades, P. Gareri, Citicolina: pharmacological and clinical review, J. Rev. Neurol., 75, 1–89, 2022.

2. J. J. Secades, Citicoline: pharmacological and clinical review, J. Rev. Neurol., 63, 1-73, 2016.

3. J. J. Secades, Citicoline: pharmacological and clinical review, J. Rev. Neurol., 52, 1-52, 2011.

4. G. B. Weiss, M. Hurley, C. Avenue, M. Hill, Minireview metabolism and actions of cdp-choline as an endogenous compound and administered exogenously as citicoline (Na Salt) Soluble in Water, J. Life Sci., 56, 637–660, 1995.

5. E. Icel, The Use of Citicoline in Ophthalmology: A systematic review, Beyoglu Eye J., 11, 1–12, 2026.

6. E. Panel, A. Nda, Scientific Opinion on the safety of "citicoline" as a Novel Food ingredient, EFSA J., 11, 1–22, 2013.

.

7. P. Zhao, B. Liu, C. Xie, Q. Li, X. Du, H. Sun, Crystallization of citicoline sodium by anti-solvent assisted with ultrasound, J. Cryst. Growth, 593, 126738, 2022.

8. F. Franks, Water: A Comprehensive Treatise, Volume 4: Aqueous Solutions of Amphiphiles and Macromolecules, Springer Science & Business Media, New York, 2013.

9. P. Y. Umredkar, V. M. Tangde, N. T. Khaty, S. S. Yelekar, N. Sapkal, S. S. Dhondge, Unraveling the Solvation Behavior of Levocetirizine Dihydrochloride: Insights from Volumetric, Acoustic, Viscometric, and Electronic Absorption Studies in Aqueous L-Proline and L-Valine Solutions, J. Chem. Eng. Data, 69, 915-932, 2024.

10. H. Kumar, I. Behal, S. Siraswar, Densities and Speeds of Sound for Sucrose in Aqueous Solutions of Ammonium Phosphate Salts at Different Temperatures through Density and Speed of Sound Measurements, J. Chem. Eng. Data, 64, 3772–3780, 2019.

11. D. M. Bhattacharya, D. V Kawadkar, C.P. Pandhurnekar, A. V Wankhade, U.R. Pratap, S.P. Zodape, Investigation of Volumetric and Acoustic Properties of Procainamide Hydrochloride in Aqueous Binary and (Water + Amino Acid) Ternary Mixtures at Different Temperatures, J. Chem. Eng. Data, 62, 4083–4092, 2017.

12. S. K. Lomesh, V. Nathan, M. Bala, P. Thakur, Volumetric and acoustic methods for investigating molecular interactions of antibiotic drug doxycycline hyclate in water and in aqueous solution of sodium chloride and potassium chloride at different temperatures (293.15–313.15) K, J. Mol. Liquid, 284, 241–251, 2019.

13. J. Millero, The Apparent and Partial Molal Volume of Aqueous Sodium Chloride Solutions, J. Phys. Chem. 74, 356–362, 2001.

14. K. M. Jamkhande, N. T. Khaty, C. P. Pandhurnekar, R. R. Ugale, V. M. Tangde, Physicochemical and computational aspects of duloxetine hydrochloride in aqueous methionine and alanine, J. Mol. Liquid, 448, 129391, 2026.

15. T. S. Banipal, H. Singh, P. K. Banipal, Volumetric and Viscometric Properties of Some Sulpha Drugs in Aqueous Solutions of Sodium Chloride at *T* (288.15 to 318.15) K, J. Chem. Eng. Data, 55, 3872–3881, 2010.

16. S. P. Jengathe, S. S. Dhondge, L. J. Paliwal, V. M. Tangde, Molecular interactions of sodium salicylate in physiological media under the influence of electrolyte/non-electrolyte at different temperatures: Volumetric and acoustic study, J. Chem. Thermodynamics, 115, 221–232, 2017.

17. V. M. Tangde, N. T. Khaty, S. T. Bankar, L. Malladi, N. G. Sheikh, S. S. Dhondge, A. S. Dhondge, Effect of NaCl and KCl on volumetric and acoustic behavior of aqueous Creatinine Hydrochloride solutions at *T* = (288.15–318.15) K, J. Mol. Liquid, 335, 116194, 2021.

.

18. L. Dunn, Apparent Molar Volumes of Electrolytes Part 3 -Some 1-1 and 2-1 Electrolytes in Aqueous Solution at 0, 5, 15, 35, 45, 55 and 65°C, J. Trans. Faraday Soc., 64, 2951–2961, 1968.

19. L. M. Gedansky, L.G. Hepler, Thermochemistry of the aqueous manganous ion, Can. J. Chem., 47, 699–701, 1969.

20. S. S. Dhondge, S. P. Zodape, D. V Parwate, Volumetric and viscometric studies of some drugs in aqueous solutions at different temperatures, J. Chem. Thermodynamics, 48, 207–212, 2012.

21. N. Devunuri, N. Amminabavi, B. Kumar, The structural effect on volumetric and acoustic properties of aqueous anti-HIV drugs (Emtricitabine and Lamivudine) at various temperatures, J. Mol. Liquid, 214, 10–15, 2015.

.

.