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# Thermodynamic Interaction of Quinolone (levofloxacine) Drug in Aqueous Amino Acid Solutions at around Body Temperatures

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**Abstract—***In this biophysical sytem we have investigated the volumetric, ultrasonic and viscometric behaviour of Levofloxacin (LF) in 0.0201 molal (mol·kg-1) aqueous solution of L-aspartic acid (Asp) and L-glutamic acid (Glu) at 303.15, 308.15 and 313.15K. (Close to body temperature). Apparent molar volumes (Vφ), Partial molal volume ($V^o_2$), adiabatic compressibility ($\beta_s$), B-coefficient and hydration number ($H_n$) of these solutions have been computed from density, ultrasonic velocity and viscosity data. The results areinterpreted in terms of solute-solvent interactions in quinolone - amino acids- water system.*

**Keywords:** *Partial molal volume ($V^o_2$), Adiabatic compressibility ($\beta_s$), B-coefficient, Hydration number ($H_n$), Levofloxacin andAmino acids.*

## 1. INTRODUCTION

The area of quinolones began with the introduction of nalidixic acid in 1962 for treatment of kidney infections in humans. Quinolones are the most commonly prescribed antibacterial drugs now a days in clinical use.[1] These drugs are used to treat a wide range of Gram-negative and Gram-positive bacterial infections. Several quinolones have been approved for use in the USFDA, including ciprofloxacin, levofloxacin, moxifloxacin and sparfloxacin.[2-6]Quinolone usage is becoming threatened by an increasing precedence of resistance, which currently extends to nearly every bacterial infection treated by this drug class.[4,5]In present work Levofloxacine was used as a quinolone drug to interact with acidic amino acids.

Levofloxacin (LF), (-)-(S) -9 -fluoro-2,3 -dihydro-3 -methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H pyrido [1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemi-hydrate, (Fig. 1) is one of the commonly used fluoroquinolone antimicrobials, is the active S-isomer isolated from the racemic ofloxacin. Because of excellent antibacterial activity and low frequency of adverse effects on oral administration, levofloxacin has been widely used for the treatment of infectious diseases, such as community-acquired pneumonia and acute exacerbation of chronic bronchitis.[7]

Thermodynamic methods are well recognized and convenient for studying the molecular interactions in fluids. The partial molar volume and pressure derivative of Gibbs energy are useful parameters for interpreting solute-solvent interactions.[8, 9] Comparison of the volume of the system with those of its components can assess gross changes in the volume of the system because it is an additive property. In addition, volumetric data can also be interpreted in terms of molecular interactions within the system. Various molecular processes in solutions such as electrostriction,[10]hydrophobic hydration[11] and co-sphere overlap during solute-solute interactions have been interpreted to a large extent, from the partial molar volume data of many compounds including amino acids, peptides and also some drug compounds[8].In the case of drug-protein binding, anomalous behaviour has been observed with respect to certain drugs.[12]Perceptible thermodynamic changes are found to be associated with the processes of drug transport,[13] drug-protein binding,[14] anaesthesia,[15] etc. Consequently, it is imperative that each component of these systems may be studied individually before going to more complex systems.

In this biophysical sytem we have investigated the volumetric, ultrasonic and viscometric behaviour of Levofloxacin (LF) in aqueous and 0.0201 molal (mol·kg -1) aqueous solution of L-aspartic acid (Asp) and L-glutamic acid (Glu) at 303.15, 308.15 and 313.15K. (Close to body temperature) with help of this study we have tried to understand the interaction of drug with amino acids at body temperature, and drug-macromolecular interaction phenomenon involving complex

molecular mechanism associated with the structure of bio-macromolecules or with their data interpretation.

## 2. MATERIAL AND METHODS

L-glutamic acid (Glu)and L-aspartic acid (Asp) of high purity obtained from Sisco Research Laboratories, (India), while Levofloxacin (LF) was purchased from Morepen Laboratory Ltd. (India). All solvents and chemicals were of analytical grade. These chemicals were used without further purification. The triplicate distilled water (with the specific conductivity of $1.29\times10^{-6}\ \Omega^{-1}.cm^{-1}$) was used for making all the amino acid solutions and thestock solution. All the solutions were stored in special airtight bottles to avoid exposure of solutions to air and evaporations.

### 2.1. Density measurements

Densities ($\rho$) of Levofloxacin (LF) in aqueous and amino acid (Asp and Glu) solutions were measured using a single-capillary pycnometer (made of Borosilicate glass) having a bulb capacity ~ $9cm^3$ the method describes elsewhere.[16] The uncertainty found in density measurement was within ± 0.02 $kg{\cdot}m^{-3}$.

### 2.2. Ultrasonic measurements

The ultrasonic velocity ($U$) of Levofloxacin (LF) in aqueous and amino acid (Asp and Glu) solutions was measured by using single-crystal variable-path multi-frequency ultrasonic interferometer (Model: M-84, Mittal Enterprises, Delhi, India) with stainless steel sample cell operating at 2MHz.as described elsewhere.[17]The uncertainty in ultrasonic velocity measurement was within 0.03 %.

### 2.3. Viscosity measurement

The viscosity ($\eta$) of Levofloxacin (LF) in aqueous and amino acid (Asp and Glu) solutions was measured by using ubbelohde type suspended level viscometer. The working procedure is described elsewhere.[18]The uncertainties in viscosity measurements have been found to be within ± 0.003 mPa·s.

The triplicate reproducibility has been checked during all this experiment work. The thermostatic paraffin bath (JULABO, Model-MD Germany) used during the measurements of density and viscosity was maintained at desired temperature (± 0.02 K) for about 30 min. prior to record of reading at each temperature of study. The weighing was done on electronic balance (model: GR-202R, AND Japan) with the precision of ± 0.01mg. The uncertainty in molal concentration values have been found to be within $1.0\times10^{-4}\ mol{\cdot}kg^{-1}$.

## 3. RESULT AND DISCUSSIONS

The apparent molal volume*($V\varphi$)*, of Levofloxacin (LF) in aqueous and in 0.0201 molal ($mol\,kg^{-1}$) aqueous solution of amino acids (Asp and Glu) at 303.15, 308.15 and 313.15 K were determined from experimental density value (given in Table 1, 2 and 3) by using the following equations;

$$V\varphi = (M/\rho) - 1000\,[(\rho - \rho_o)/(m.\rho.\rho_o)] \quad (1)$$

where $\rho$, and $\rho_o$are densities of solution (LF + solvent ) and the solvent (water + amino acids or water) respectively, m is the molality ($mol{\cdot}kg^{-1}$) and M is molar mass of true solute. The values of apparent molar volume are mentioned in Table 1. The values of $V\varphi$, in the water-amino acid system are comparatively higher than those of pure water (shown in Fig. 2, 3 and 4). The values of apparent molal volume at infinite dilution ($V^o_2$) are computed with help of linear plot of $V\varphi$ against the molality, (m) with the help of following equations;

$$V\varphi = V^o_2 + S_v\, m \quad (2)$$

$$\Delta V_{tr} = V^o_2(\text{in ternary solutions}) - V^o_2\,(\text{in water}) \quad (3)$$

where $V^o_2$is the apparent molar volume at infinite dilution also known as standard partial molal volumeand $S_v$ is the experimental slope, $\Delta V_{tr}$ is standard transfer volume.

Standard partial molal volume and standard transfer volume values are summarized in Table 4. Positive values of $V^o_2$ indicate that this does not restrict molecular motion within the solution. The value of $V^o_2$ increases with the increase of temperature. Ion-ion interactions resultin positive $\Delta V_{tr}$ values, whereas ion-hydrophobic and hydrophobic-hydrophobic group interactions result in negative $\Delta V_{tr}$ values according to the co-sphere model.[19] The present study observed higher $V^o_2$values of Levofloxacin (drug) for amino acids solutions as compared with their values in water suggest that ion-ion interactions dominate the ion-hydrophobic and hydrophobic-hydrophobic interactions.

The adiabatic compressibility ($\beta_s$) of Levofloxacin (LF)in aqueous (Table 1) and in 0.0201 molal ($mol\,kg^{-1}$) aqueous solution of amino acids (Asp and Glu) at temperatures (303.15 to 313.15) K were determined (Table 2 and 3) from experimental ultrasonic velocity and density value (both are given in Table 1) by using Newton-Laplace,[20] equation given below;

$$\beta_s = 1/\rho{\cdot}U^2 \quad (4)$$

where all the symbols have their usual meaning. The values of adiabatic compressibility ($\beta_s$) (listed in Table1) are function of concentration ($mol{\cdot}kg^{-1}$) and temperature of Levofloxacin. The study on quinolone concluded that the drug stays as zwitter ions due to ionization of carboxylic group and protonation of piperazinyl group.[21] The values of adiabatic compressibility decreasewith the increase in temperature and concentration of Levofloxacin (LF)in 0.0201 $mol{\cdot}kg^{-1}$ (or molal, both have the same meaning) aqueous solution of both L-aspartic and L-glutamic acid (shown in Figure5, 6 and 7) may be due to (i) an increase in the number of incompressible molecules/zwitterions in solutions and (ii) the formation of compact structure of zwitterions–water dipole and zwitterion-zwitterion structures in solutions. The decrease in adiabatic

compressibility values with an increase in temperature in all the systems under investigation may be attributed to the corresponding decrease of the relaxational part of compressibility ($\beta_{relax}$), which is dominant over the corresponding increase of instantaneous part of compressibility($\beta_{\infty}$).[22,23]

The adiabatic compressibility values of LF in 0.0201 mol·kg$^{-1}$ aqueous aspartic acid and glutamic acids are less than that of water in the temperature range of *T* (303.15 to 313.15) K. The smaller values of $\beta_s$for the said amino acid solutions than that of water may be attributed to ions-water dipoles and ion-zwitterion interactions in the solutions, which ultimately may lead to an overall increase in cohesive forces in solutions.

The experimental values of viscosity ($\eta$) are measured at different temperatures for LF in aqueous and in two different amino acid (asp and glu) solutions (listed in Table 1). The viscosity data of these solutions are used to calculate the B coefficient with the help of well known Jones-Dole[24]equations shown below,

$$\eta_r = \eta / \eta_o = 1 + A\sqrt{m} + Bm \quad (5)$$

where m is the concentration (mol·kg$^{-1}$), η and $\eta_o$ are the viscosities of solution and solvent respectively, $\eta_r$ is the relative viscosity of the solution.The *B*-coefficients value has been given in Table 4.

Viscosity data are analysed in the terms of Jones-Dole equations. Positive *B* values indicate a strong alignment of solvent molecules with those of the solute.[25-29]*B* values decrease with rise in temperature, (as shown in Table4) to indicate the structure-promoting tendency of compound. The hydration of solute is judged from the value of the hydration number, ($H_n$), which can be calculated by the following expression;[30]

$$H_n = B / V^o{}_2 \quad (6)$$

The observed values of $H_n$ < 2.5at low temperatures (Table 4) indicate that levofloxacin in not very hydrated in aqueous as well as amino acids solution because a value higher than $H_n$ = 2.5 is an indication of hydrated species.[30]

### 3.1. Tables

**Table 1: Density($10^{-3}\rho$/Kg·m$^{-3}$), viscosity ($10^{-3}\eta$/N·s·m$^{-2}$), ultrasonic velocity (*U*/m·s$^{-1}$) adiabatic compressibility ($10^{-11}\beta_s$/m$^2$·N$^{-1}$)and apparent molar volume ($10^6 V\varphi$/m$^3$·mol$^{-1}$) of Levofloxacin (LF) in aqueous solutions at *T* = (303.15 to 313.15) K.**

| Levofloxacin (LF) in aqueous solution | | | | | | |
|---|---|---|---|---|---|---|
| T/K | ma | ρb | Vφc | U d | βs e | ηf |
| 303.15 | 0.0201 | 0.99601 | 342.24 | 1510.56 | 44.00 | 0.8016 |
| | 0.0402 | 0.99640 | 342.48 | 1513.96 | 43.80 | 0.8108 |
| | 0.0604 | 0.99679 | 342.67 | 1516.66 | 43.60 | 0.8205 |
| | 0.0808 | 0.99716 | 342.94 | 1518.87 | 43.50 | 0.8486 |
| | 0.1010 | 0.99750 | 343.33 | 1521.22 | 43.30 | 0.8662 |
| | | | | | | |
| 308.15 | 0.0201 | 0.99440 | 343.26 | 1521.85 | 43.40 | 0.7208 |
| | 0.0402 | 0.99479 | 343.38 | 1524.03 | 43.30 | 0.7347 |
| | 0.0604 | 0.99517 | 343.53 | 1525.22 | 43.20 | 0.7537 |
| | 0.0808 | 0.99554 | 343.72 | 1527.02 | 43.10 | 0.7878 |
| | 0.1010 | 0.99590 | 343.85 | 1529.72 | 42.90 | 0.8061 |
| | | | | | | |
| 313.15 | 0.0201 | 0.88260 | 343.85 | 1529.50 | 43.10 | 0.6598 |
| | 0.0402 | 0.99299 | 343.97 | 1530.26 | 43.00 | 0.6690 |
| | 0.0604 | 0.99337 | 344.12 | 1531.06 | 42.90 | 0.6859 |
| | 0.0808 | 0.99374 | 344.31 | 1533.25 | 42.80 | 0.6975 |
| | 0.1010 | 0.99410 | 344.44 | 1535.01 | 42.70 | 0.7154 |

**Table 2: Density($10^{-3}\rho$/Kg·m$^{-3}$), viscosity ($10^{-3}\eta$/N·s·m$^{-2}$), ultrasonic velocity (*U*/m·s$^{-1}$) adiabatic compressibility ($10^{-11}\beta_s$/m$^2$·N$^{-1}$)and apparent molar volume ($10^6 V\varphi$/m$^3$·mol$^{-1}$) Levofloxacin (LF) in aqueous solution of Aspartic acid at *T* = (303.15 to 313.15) K.**

| Levofloxacin(LF) in aspartic acid solution (me = 0.0201) | | | | | | |
|---|---|---|---|---|---|---|
| T/K | ma | ρb | Vφc | U d | βs e | ηf |
| 303.15 | 0.0200 | 0.99696 | 355.42 | 1515.73 | 43.70 | 0.8407 |
| | 0.0401 | 0.99708 | 355.80 | 1517.93 | 43.52 | 0.8528 |
| | 0.0603 | 0.99720 | 355.92 | 1518.53 | 43.50 | 0.8613 |
| | 0.0806 | 0.99731 | 356.22 | 1522.90 | 43.20 | 0.8765 |
| | 0.1014 | 0.99742 | 356.35 | 1524.93 | 43.10 | 0.8896 |
| | | | | | | |
| 308.15 | 0.0200 | 0.99530 | 358.27 | 1525.22 | 43.20 | 0.7746 |
| | 0.0401 | 0.99538 | 358.61 | 1526.60 | 43.10 | 0.7922 |
| | 0.0603 | 0.99546 | 358.83 | 1528.60 | 43.00 | 0.7951 |
| | 0.0806 | 0.99553 | 358.98 | 1531.26 | 42.85 | 0.8111 |
| | 0.1014 | 0.99558 | 359.28 | 1532.00 | 42.80 | 0.8321 |
| | | | | | | |
| 313.15 | 0.0200 | 0.99350 | 359.07 | 1530.16 | 43.01 | 0.6848 |
| | 0.0401 | 0.99358 | 359.17 | 1531.20 | 42.90 | 0.6938 |
| | 0.0603 | 0.99367 | 359.26 | 1532.90 | 42.80 | 0.6995 |
| | 0.0806 | 0.99375 | 359.34 | 1536.76 | 42.60 | 0.7145 |
| | 0.1014 | 0.99388 | 359.39 | 1538.50 | 42.50 | 0.7482 |

**Table 3: Density($10^{-3}\rho$/Kg·m$^{-3}$), viscosity ($10^{-3}\eta$/N·s·m$^{-2}$), ultrasonic velocity (*U*/m·s$^{-1}$) adiabatic compressibility ($10^{-11}\beta_s$/m$^2$·N$^{-1}$)and apparent molar volume ($10^6 V\varphi$/m$^3$·mol$^{-1}$) Levofloxacin (LF) in aqueous solution of Glutamic acid at *T* = (303.15 to 313.15) K.**

| Levofloxacin (LF) in glutamic acidsolution (m = 0.0201) | | | | | | |
|---|---|---|---|---|---|---|
| T/K | ma | ρb | Vφc | U d | βs e | ηf |
| 303.15 | 0.0201 | 0.99690 | 354.46 | 1514.63 | 43.70 | 0.8192 |
| | 0.0402 | 0.99705 | 354.62 | 1519.30 | 43.50 | 0.8246 |
| | 0.0605 | 0.99720 | 354.73 | 1521.46 | 43.30 | 0.8332 |
| | 0.0811 | 0.99734 | 354.88 | 1524.26 | 43.20 | 0.8575 |
| | 0.1015 | 0.99746 | 355.15 | 1526.83 | 43.00 | 0.8705 |
| | | | | | | |
| 308.15 | 0.0201 | 0.99528 | 355.64 | 1522.10 | 43.30 | 0.7386 |
| | 0.0402 | 0.99543 | 355.69 | 1524.16 | 43.20 | 0.7428 |
| | 0.0605 | 0.99557 | 355.73 | 1529.16 | 43.00 | 0.7513 |
| | 0.0811 | 0.99571 | 355.80 | 1531.80 | 42.80 | 0.7714 |
| | 0.1015 | 0.99584 | 355.87 | 1536.13 | 42.60 | 0.8139 |
| | | | | | | |
| 313.15 | 0.0201 | 0.99349 | 356.67 | 1530.76 | 43.00 | 0.6821 |
| | 0.0402 | 0.99362 | 356.88 | 1532.33 | 42.90 | 0.6873 |
| | 0.0605 | 0.99374 | 357.11 | 1536.86 | 42.60 | 0.6909 |
| | 0.0811 | 0.99385 | 357.35 | 1538.00 | 42.50 | 0.6962 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 0.1015 | 0.99396 | 357.47 | 1540.63 | 42.40 | 0.7284 |

**Table 4: Partial molar volume ($10^6V^o_2$ /$m^3$·$mol^{-1}$), Standard transfer molar volume ($10^6\Delta Vtr$/$m^3$·$mol^{-1}$), Viscosity coefficient (*B*) Hydration number ($H_n$) of Levofloxacin (LF) in aqueous and aqueous solution amino acids at *T* = (303.15 to 313.15) K.**

| Levofloxacin (LF) in aqueous solution | | | | |
|---|---|---|---|---|
| **T/K** | **Vo2g** | **ΔVtrh** | **Bi** | **Hn** |
| 303.15 | 341.95 | - | 0.1384 | 0.4047 |
| 308.15 | 343.10 | - | 0.1244 | 0.3626 |
| 313.15 | 343.69 | - | 0.1198 | 0.3486 |
| Levofloxacin(LF) in aspartic acid solution (m = 0.0201) | | | | |
| 303.15 | 355.26 | 13.33 | 0.3072 | 0.8645 |
| 308.15 | 358.08 | 14.98 | 0.2668 | 0.7450 |
| 313.15 | 359.01 | 15.32 | 0.2516 | 0.7008 |
| Levofloxacin (LF) in glutamic acidsolution (m = 0.0201) | | | | |
| 303.15 | 354.28 | 12.33 | 0.1764 | 0.4979 |
| 308.15 | 355.58 | 12.48 | 0.1546 | 0.4348 |
| 313.15 | 356.48 | 12.79 | 0.1495 | 0.4194 |

[a] Molality of LF in aqueous and in amino acids solution. Units: mol·$kg^{-1}$

[b] Density of LF in aqueous and in amino acids solution. Units: $10^{-3}$,kg·$m^{-3}$

[c] Apparent molar volumes of LF in aqueous and in amino acids solution. Units: $10^6$,$m^3$·$mol^{-1}$

[d] ultrasonic velocity of LF in aqueous and in amino acids solution. Units: U/m·$s^{-1}$

[e] Adiabatic compressibility of LF in aqueous and in amino acids solution. Unit:$10^{-11}$, $m^2$·$N^{-1}$

[f] Viscosity of LF in aqueous and in amino acids solution. Units: $10^{-3}$,N·s·$m^{-2}$

[g] Partial molar volume of LF in aqueous and in amino acids solution. Units: $10^6$, $m^3$·$mol^{-1}$

[h] Standard transfer molar volume of LF in aqueous and in amino acids solution. Units: $10^6$, $m^3$·$mol^{-1}$

[i] Viscosity coefficient of LF in aqueous and in amino acids solution. Units: dm·$mol^{-1}$.

### 3.2. Figures

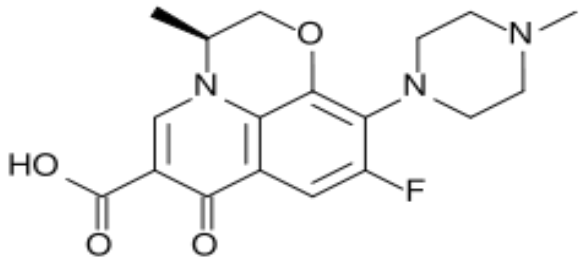


**Fig. 1: Chemical structure of Levoflaxacin (LF)**

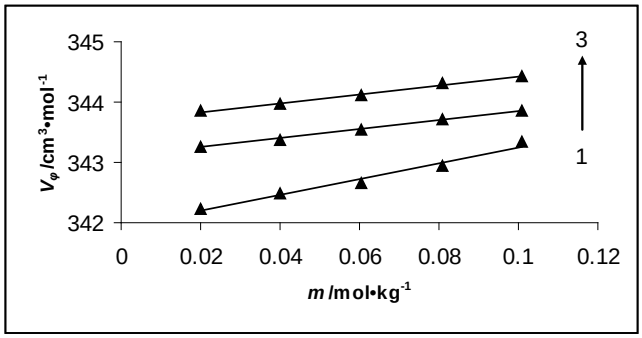


**Fig. 2: Plot of Apparent molar volume ($V\varphi$/$cm^3$·$mol^{-1}$) of Levofloxacin (LF) in aqueous solutions as a function of concentration (mol·$kg^{-1}$) at *T* = (303.15 to 313.15) K; where 1-3 stands for 1-303.15 K, 2-308.15 K and 3-313.15 K.**

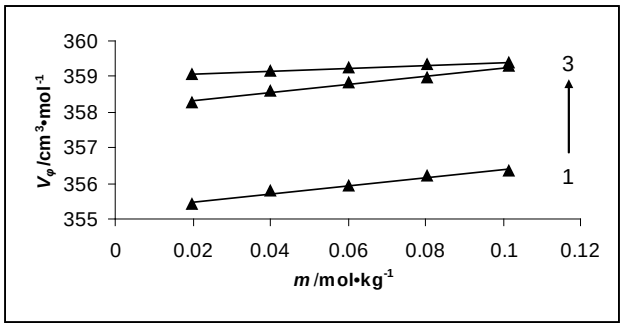


**Fig. 3: Plot of Apparent molar volume ($V\varphi$/$cm^3$·$mol^{-1}$) of Levofloxacin (LF) in aqueous solution of L-aspartic acid (m = 0.0201mol·$kg^{-1}$) as a function of concentration (mol·$kg^{-1}$) at *T* = (303.15 to 313.15) K; where 1-3 stands for 1-303.15 K, 2-308.15 K and 3-313.15 K.**

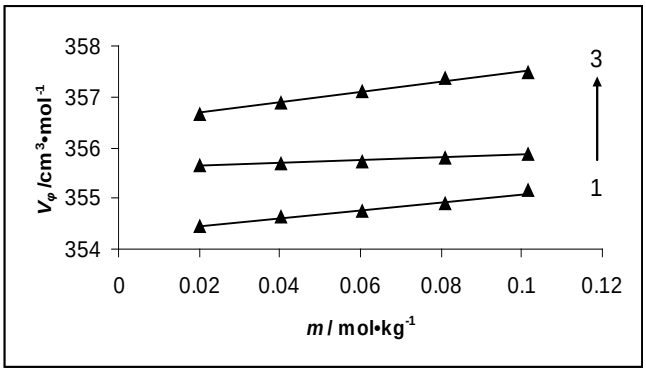


**Fig. 4: Plot of Apparent molar volume ($V\varphi$/$cm^3$·$mol^{-1}$) of Levofloxacin (LF) in aqueous solution of L-glutamic acid (m = 0.0201mol·$kg^{-1}$) as a function of concentration (mol·$kg^{-1}$) at *T* = (303.15 to 313.15) K; where 1-3 stands for 1-303.15 K, 2-308.15 K and 3-313.15 K.**

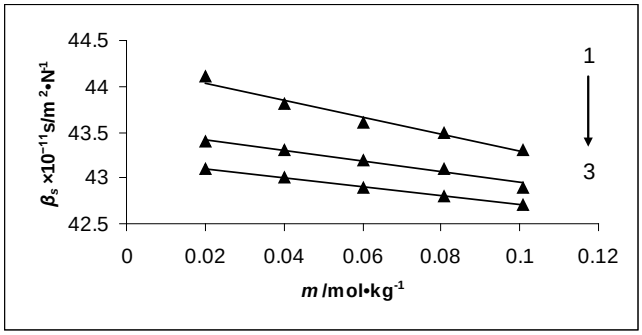


**Fig. 5: Plot of Adiabatic compressibility ($\beta_s \times 10^{-11}{}_s$/m$^2$·N$^{-1}$) of Levofloxacin (LF) in aqueous solution as a function of concentration (mol·kg$^{-1}$) at *T* = (303.15 to 313.15) K; where 1-3 stands for 1-303.15 K, 2-308.15 K and 3-313.15 K.**

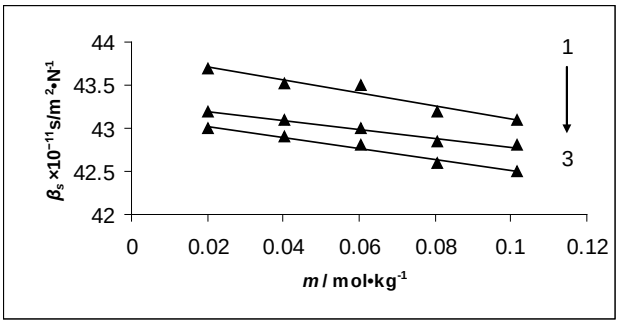


**Fig. 6: Plot of Adiabatic compressibility ($\beta_s \times 10^{-11}{}_s$/m$^2$·N$^{-1}$) of Levofloxacin (LF) in aqueous solution of L-aspartic acid (m = 0.0201mol·kg$^{-1}$) as a function of concentration (mol·kg$^{-1}$) at *T* = (303.15 to 313.15) K; where 1-3 stands for 1-303.15 K, 2-308.15 K and 3-313.15 K.**

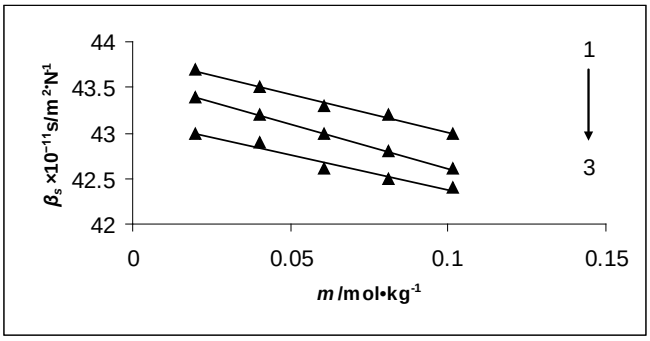


**Fig. 7: Plot of Adiabatic compressibility ($\beta_s \times 10^{-11}{}_s$/m$^2$·N$^{-1}$) of Levofloxacin (LF) in aqueous solution of L-glutamic acid (m = 0.0201mol·kg$^{-1}$) as a function of concentration (mol·kg$^{-1}$) at *T* = (303.15 to 313.15) K; where 1-3 stands for 1-303.15 K, 2-308.15 K and 3-313.15 K.**

## 4. CONCLUSION

In summary, we have presented volumetric, ultrasonic and viscometric properties of Quinolone drug, namely, levofloxacin in aqueous and aqueous amino acid (Asp and Glu) solutions. The density values increase with an increase in molality of solute (drug) and decrease with an increase in temperature for the systems under investigation. The adiabatic compressibility decreases with an increase in the levofloxacin concentration as well as temperature. The values of the partial molar volume in dilute aqueous solutions are positive, indicating strong solute-solvent interactions. The results of Jones-Dole viscosity B-coefficients of these drugs are also positive which is indicating a structure-promoting tendency between drug and amino acids.

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