



# Experimental Investigation of Acoustic Properties and Molecular Interactions of Vadadustat in Aqueous–Organic Solvent Mixtures at 300 K

Usha S Wasnik

Department of Chemistry, Arts ,Science & commerce & College, Chikhaldara

Dist : Amravati(M.S.) India

\*Corresponding author [us.wasnik@gmail.com](mailto:us.wasnik@gmail.com)

## Abstract

*The present study investigates the acoustic and thermodynamic properties of Vadadustat in selected solvent media at 300K to understand drug–solvent molecular interactions. Ultrasonic velocity, density and viscosity measurements will be carried out at different concentrations of Vadadustat. Various acoustic and thermodynamic parameters, including adiabatic compressibility, intermolecular free length, acoustic impedance, apparent molar volume, apparent molar compressibility, relative association and excess properties, will be evaluated from the experimental data. The concentration dependence of these parameters will be analysed to elucidate solute–solvent and solvent–solvent interactions, particularly hydrogen bonding and structural effects. The study is expected to provide useful insights into the solution-state behaviour and physicochemical characteristics of Vadadustat and demonstrate the utility of ultrasonic techniques for investigating molecular interactions in pharmaceutical systems.*

**Keywords:** Vadadustat; ultrasonic velocity, acoustic properties, thermodynamic properties, molecular interactions, hydrogen bonding

## Introduction

The investigation of molecular interactions in pharmaceutical solutions is important in solution chemistry, pharmaceutical sciences and drug-development research. The physicochemical behaviour of a drug in solution depends on solute–solvent and solute–solute interactions, hydrogen bonding, hydration, molecular association and changes in solvent structure. Acoustic and thermodynamic techniques are particularly useful for studying such interactions because ultrasonic velocity, density and viscosity are sensitive to molecular organization, compressibility and intermolecular forces. Recent studies have established the usefulness of ultrasonic methods for investigating molecular structure, intermolecular interactions and thermodynamic properties of binary and multicomponent liquid systems [1,2].

Ultrasonic measurements, combined with density and viscosity data, permit the evaluation of important parameters such as adiabatic compressibility, intermolecular free length, acoustic impedance, apparent molar

volume and related excess properties. Variations in these parameters with concentration provide valuable information about the nature and strength of molecular interactions. In pharmaceutical systems, volumetric and ultrasonic parameters have been successfully employed to distinguish hydration, hydrogen bonding, hydrophilic and hydrophobic contributions to solute–solvent interactions [3–6]. Studies of drug-containing solutions have further shown that apparent molar volume, apparent molar isentropic compressibility and viscosity-related parameters can provide information about solvation, hydration and structure-making or structure-breaking behaviour [6–8].

Vadadustat, chemically identified as 2-[[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl] amino] acetic acid, is a small-molecule hypoxia-inducible factor prolyl hydroxylase (HIF-pH) inhibitor developed for the treatment of anaemia associated with chronic kidney disease. Its molecular formula is  $C_{14}H_{11}ClN_2O_4$  and molecular mass is  $306.70 \text{ g mol}^{-1}$ . The molecule contains hydroxyl, carboxylic acid, amide and pyridine nitrogen functionalities together with a chlorophenyl group. These structural features provide several potential sites for hydrogen bonding, dipolar interactions, hydration and hydrophobic association, making Vadadustat an interesting compound for acoustic and thermodynamic investigations.

The acid–base behaviour and possible zwitterionic character of Vadadustat further increase the complexity of its solution chemistry. Its protonation equilibria and ionizable functional groups can influence hydration, molecular association and solute–solvent interactions. Consequently, the acoustic response of Vadadustat solutions may reflect a combination of hydrogen bonding, ionic interactions, solvent restructuring and hydrophobic effects. Its relatively limited aqueous solubility also emphasizes the importance of understanding its solution-state behaviour.

Previous ultrasonic investigations of pharmaceutical compounds have demonstrated that measurements of density, ultrasonic velocity and viscosity, followed by evaluation of derived acoustic and thermodynamic parameters, can provide meaningful information about molecular interactions. Similar approaches have been successfully applied to drugs such as metformin hydrochloride, cefpodoxime acid and other pharmaceutical systems [9–11]. Measurements at 300 K provide a well-defined reference condition for examining concentration-dependent physicochemical behaviour and comparing molecular interactions under controlled conditions.

In the present study, Vadadustat solutions are investigated at 300 K over an appropriate concentration range using ultrasonic velocity, density and viscosity measurements. The experimental data are employed to evaluate adiabatic compressibility, intermolecular free length, acoustic impedance, apparent molar volume, apparent molar compressibility and selected thermodynamic parameters. The concentration dependence of these quantities is interpreted in terms of solute–solvent and solute–solute interactions, hydrogen bonding, hydration, ionic interactions and hydrophobic association. The study is expected to provide useful experimental information on the molecular interactions and solution behaviour of Vadadustat and thereby contribute to its physicochemical characterization.

## Theory

Acoustic parameters such as apparent molar compressibility ( $\phi_k$ ), apparent molar volume ( $\phi_v$ ), adiabatic compressibility ( $\beta_s$ ), specific acoustic impedance ( $Z$ ), intermolecular free length ( $L_f$ ), Limiting apparent molar volume ( $\phi^0$ ) Limiting apparent molar compressibility ( $\phi^0$ ) were determined using following relations.

|                                         |                                                                                       |       |   |
|-----------------------------------------|---------------------------------------------------------------------------------------|-------|---|
| Ultrasonic velocity                     | $u = \lambda \nu$                                                                     | ----- | 1 |
| Adiabatic compressibility               | $\beta_s = 1/u^2 \rho_s$                                                              | ----- | 2 |
| Apparent molar volume                   | $\phi_v = 10^3(\rho_0 - \rho_s)/m - \rho_0 \rho_s + M/\rho_0$                         | ----- | 3 |
| Apparent molar compressibility          | $\phi_k = 10^3(\rho_0 \beta_s - \rho_s \beta_0)/m - \rho_s \rho_0 + \beta_s M/\rho_s$ | ----- | 4 |
| Intermolecular free length              | $L_f = K (\beta_s)^{1/2}$                                                             | ----- | 5 |
| Specific acoustic impedance             | $Z = \rho \cdot u$                                                                    | ----- | 6 |
| Limiting apparent molar volume          | $\phi_v = \phi^0 + S_v C^{1/2}$                                                       | ----- | 7 |
| Limiting apparent molar compressibility | $\phi_k = \phi^0 + S_k C^{1/2}$                                                       | ----- | 8 |

**Table no.1**

**Experimental Data of Density, Ultrasonic Velocity and Viscosity of Vadadustat different solvent at 300K**

| Solvents                     | Conc. mol.dm <sup>-3</sup> | Density<br>Kg m <sup>-3</sup> | Ultrasonic<br>Velocity( $u_s$ ) m/s | Viscosity<br>N s m <sup>-2</sup> $\times 10^{-3}$ |
|------------------------------|----------------------------|-------------------------------|-------------------------------------|---------------------------------------------------|
| 30% MeOH-<br>Water Medium    | 0.001                      | 972.17                        | 1532.25                             | 1.3688                                            |
|                              | 0.002                      | 972.35                        | 1537.21                             | 1.3720                                            |
|                              | 0.003                      | 972.49                        | 1541.33                             | 1.3754                                            |
| Water Medium                 | 0.004                      | 972.71                        | 1546.44                             | 1.3776                                            |
|                              | 0.005                      | 972.87                        | 1549.85                             | 1.3798                                            |
| 30% Dioxane-<br>Water Medium | 0.001                      | 1121.56                       | 1362.58                             | 1.3123                                            |
|                              | 0.002                      | 1126.12                       | 1366.84                             | 1.3165                                            |
|                              | 0.003                      | 1132.05                       | 1371.82                             | 1.3198                                            |
|                              | 0.004                      | 1137.94                       | 1375.13                             | 1.3234                                            |
|                              | 0.005                      | 1142.65                       | 1379.66                             | 1.3272                                            |
| 30% DMF-<br>Water Medium     | 0.001                      | 1001.34                       | 1478.3                              | 2.1234                                            |
|                              | 0.002                      | 1006.25                       | 1480.4                              | 2.1260                                            |
|                              | 0.003                      | 1012.54                       | 1482.1                              | 2.1291                                            |
|                              | 0.004                      | 1019.87                       | 1484.3                              | 2.1322                                            |
|                              | 0.005                      | 1025.28                       | 1485.6                              | 2.1351                                            |

Table no.2

Variation of some acoustical parameters with concentration of Vadadustat in different solvents at 300 K

| $\Phi_v$<br>Solvents<br>$\times 10^{11} \text{m}^3 \text{mol}^{-1}$ | Conc.mol.dm <sup>-3</sup> | $\beta_s \times 10^{-10} \text{ } ^{-1} \text{Pa}$ | $\Phi_k \text{ x m}^3 \text{mol}^{-1} \text{ } ^{-1} \text{Pa}^{-1}$ | $L_f \text{ (m)}$ | $Z \times 10^5 \text{Kg m}^{-2} \text{sec}^{-1}$ |          |
|---------------------------------------------------------------------|---------------------------|----------------------------------------------------|----------------------------------------------------------------------|-------------------|--------------------------------------------------|----------|
| 30% MeOH-Water<br>Medium                                            | 0.01                      | 4.38125                                            | 9.14547                                                              | -60.9573230       | 1.262224                                         | 14.89607 |
|                                                                     | 0.002                     | 4.35222                                            | 4.57273                                                              | -70.1584500       | 1.258035                                         | 14.94706 |
|                                                                     | 0.003                     | 4.32836                                            | 3.04848                                                              | -76.7538496       | 1.254582                                         | 14.98928 |
|                                                                     | 0.004                     | 4.29883                                            | 2.28636                                                              | -85.6378909       | 1.250299                                         | 15.04237 |
|                                                                     | 0.005                     | 4.27923                                            | 1.82909                                                              | -91.5570884       | 1.247446                                         | 15.07802 |
| 30% Dioxane-Water<br>Medium                                         | 0.001                     | 4.80235                                            | 11.86423                                                             | -218.46613        | 1.321495389                                      | 15.28215 |
|                                                                     | 0.002                     | 4.75313                                            | 5.93199                                                              | -250.18964        | 1.31470678                                       | 15.39225 |
|                                                                     | 0.003                     | 4.69397                                            | 3.95466                                                              | -289.70090        | 1.306498705                                      | 15.52968 |
|                                                                     | 0.004                     | 4.64722                                            | 2.96599                                                              | -324.05218        | 1.299976435                                      | 15.64815 |
|                                                                     | 0.005                     | 4.59772                                            | 2.37279                                                              | -357.12074        | 1.293034859                                      | 15.76468 |
| 30% DMF-Water<br>Medium                                             | 0.01                      | 3.93963                                            | 9.86048                                                              | -44.61056234      | 1.196924846                                      | 15.94273 |
|                                                                     | 0.002                     | 3.91004                                            | 4.93023                                                              | -60.87265062      | 1.192420808                                      | 16.04214 |
|                                                                     | 0.003                     | 3.8751                                             | 3.28682                                                              | -80.96778541      | 1.187080642                                      | 16.16459 |

|       |         |         |              |             |          |
|-------|---------|---------|--------------|-------------|----------|
| 0.004 | 3.83609 | 2.46511 | -104.1331183 | 1.181090662 | 16.30527 |
| 0.005 | 3.80347 | 1.97209 | -122.701783  | 1.176057888 | 16.41842 |

**Table-3**

Limiting values of  $\phi_v$  and  $\phi_k$  along with slope ( $S_v$  &  $S_k$ ) for Vadadustat in different medium at 300K temperature

| Temp. T (K) | Medium    | Parameters                                             |                                                                         |                                                                      |                                                                                       |
|-------------|-----------|--------------------------------------------------------|-------------------------------------------------------------------------|----------------------------------------------------------------------|---------------------------------------------------------------------------------------|
|             |           | $\phi_v^0 \times 10^{-5} \text{ m}^3 \text{ mol}^{-1}$ | $\phi_k^0 \times 10^{-14} \text{ m}^3 \text{ mol}^{-1} \text{ pa}^{-1}$ | $S_v \times 10^{-5} \text{ m}^3 \text{ mol}^{-3/2} \text{ dm}^{3/2}$ | $S_k \times 10^{-14} \text{ m}^3 \text{ mol}^{-3/2} \text{ dm}^{3/2} \text{ pa}^{-1}$ |
| 300K        | 30% M-W   | -1.6919                                                | -786.94                                                                 | 9.2522                                                               | 35.296                                                                                |
|             | 30% D-W   | -236.15                                                | -3585                                                                   | 17.937                                                               | -97.86                                                                                |
|             | 30% DMF-W | -196.27                                                | -2026.7                                                                 | 14.907                                                               | 24.784                                                                                |

**Table-4**

A and  $\beta$ , coefficient values at at 300K in different medium for Vadadustat

| Medium                   | coefficient | Temp 300 K |
|--------------------------|-------------|------------|
| 30%Methanol-Water medium | A           | 0.1108     |
|                          | $\beta$     | 0.0314     |
| 30%Dioxane-Water medium  | A           | 0.0856     |
|                          | $\beta$     | 0.0404     |
| 30% DMF-Water medium     | A           | 0.1295     |
|                          | $\beta$     | 0.0231     |

## Results and Discussion:

The experimental results indicate that the physicochemical properties of Vadadustat depend on drug concentration and solvent composition. The increase in density, ultrasonic velocity, and viscosity, accompanied by a decrease in adiabatic compressibility and intermolecular free length, suggests stronger molecular interactions and changes in solvent structure.

The molecular interactions may be attributed to hydrogen bonding, dipole–dipole interactions, hydration, and molecular association involving the hydroxyl, carboxylic acid, amide, and pyridine-nitrogen groups of Vadadustat. The chlorophenyl group may also contribute to hydrophobic interactions.

The variation in apparent molar compressibility indicates differences in solute–solvent interactions among the mixed solvent systems. The DMF–water system exhibits comparatively higher viscosity and lower compressibility, whereas the dioxane–water system shows more pronounced changes in apparent molar compressibility. The differences in the coefficients A and  $\beta$  further demonstrate the influence of solvent composition on concentration-dependent interactions.

Overall, the acoustic and volumetric properties confirm that Vadadustat exhibits significant solvent-dependent molecular interactions. These findings highlight the importance of solvent polarity, hydrogen-bonding ability, and molecular association in determining its solution behaviour.

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