

COMPARATIVE ACOUSTIC AND SOLVOLYTIC STUDIES OF SULPHADIAZINE AND SULPHADOXINE IN BINARY SOLVENT SYSTEMS

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Abstract

This study presents a comprehensive investigation of the molecular interactions between sulpha drugs (sulphadiazine and sulphadoxine) and organic solvents (ethyl alcohol, dioxane, and chloroform) through acoustic measurements. Ultrasonic velocity, density, and viscosity were measured across various concentrations at 303K, 308K, and 313K, and several derived acoustic parameters were calculated. Results demonstrate that both sulpha drugs exhibit stronger interactions with ethyl alcohol compared to dioxane and chloroform, attributed to the polar nature of ethyl alcohol facilitating hydrogen bonding and dipole-dipole interactions. Comparative analysis revealed subtle differences in the behavior of sulphadiazine and sulphadoxine, reflecting their structural variations. These findings were further corroborated by IR spectroscopic studies. The research provides valuable insights into the solute-solvent interactions of sulpha drugs, with significant implications for pharmaceutical formulation and drug delivery system development.

Keywords: Sulphadiazine; Sulphadoxine; Acoustic parameters; Molecular interactions; Solvent effects; IR spectroscopy

1. Introduction

Understanding the physicochemical properties of pharmaceutical compounds in different solvent environments is crucial for drug formulation, stability assessment, and bioavailability optimization (Patel et al., 2010; Jain & Yadav, 2012). Sulphonamides, an important class of antimicrobial agents, continue to be widely used in clinical practice for treating various bacterial infections (Mishra et al., 2015). Among these, sulphadiazine and sulphadoxine are particularly significant due to their broad-spectrum activity and distinct molecular structures.

Sulfonamide drugs such as sulphadiazine and sulphadoxine have been extensively used as antibacterial agents due to their broad-spectrum activity and chemical stability. These compounds function by interfering with folic acid synthesis in bacteria, thus arresting microbial proliferation. Despite their common mechanism of action, sulphadiazine and sulphadoxine differ significantly in their physicochemical properties, including solubility, lipophilicity, and pKa, making them suitable candidates for comparative

studies in varied solvent environments. Understanding their solvolytic behavior and molecular interactions in solution is fundamental for optimizing drug delivery systems, solubility enhancement strategies, and formulation stability.

Acoustic and solvolytic analyses offer valuable insights into solute–solvent and solute–solute interactions at the molecular level. Ultrasonic techniques, particularly measurements of ultrasonic velocity and solution density, enable the computation of thermodynamic and acoustic parameters such as adiabatic compressibility, intermolecular free length, apparent molar volume, and acoustic impedance. These parameters are indicative of the degree and nature of interactions between drug molecules and the solvent medium (Saxena et al., 2013). Solvolytic studies, on the other hand, reveal the stability and susceptibility of drug molecules toward solvent-mediated chemical transformations, especially hydrolysis or solvent-assisted degradation, which are important in pharmaceutical stability testing.

Binary solvent systems, such as ethanol–water, methanol–water, and dioxane–water, are commonly used in pharmaceutical research to simulate environments of varying polarity, dielectric constant, and hydrogen bonding capacity. These mixtures allow for the fine-tuning of solvent properties to mimic physiological conditions or formulation vehicles. Changes in the solvent composition can modulate the solvation behavior and interaction strength between solutes and solvents, offering a controlled platform to investigate molecular interactions (Kumar & Singh, 2011).

Molecular interactions between drugs and solvents play a pivotal role in determining the behavior of pharmaceutical formulations (Deshmukh et al., 2014). These interactions influence critical properties such as solubility, stability, and dissolution rate, which ultimately affect the therapeutic efficacy of drug formulations (Verma & Mishra, 2016). Despite their clinical importance, detailed investigations of the molecular behavior of sulphadiazine and sulphadoxine in different solvent environments remain limited.

Acoustic studies provide a non-destructive approach to investigate molecular interactions in liquid systems (Bhatt et al., 2012; Pandey et al., 2013). The measurement of various acoustic parameters, including ultrasonic velocity, isentropic compressibility, and intermolecular free length, offers valuable insights into the nature and strength of interactions between solute and solvent molecules (Patel & Vyas, 2009). These parameters are particularly sensitive to changes in molecular organization and can reveal subtle differences in the behavior of structurally related compounds like sulphadiazine and sulphadoxine. The present study aims to investigate and compare the molecular interactions of sulphadiazine and sulphadoxine in binary solvent systems with ethyl alcohol, dioxane, and chloroform. These solvents were selected to represent a range of polarities and hydrogen bonding capabilities, allowing for a comprehensive analysis of solvent effects on the behavior of sulpha drugs. By examining various acoustic parameters across different concentrations and temperatures, this research seeks to elucidate the nature of solute-solvent interactions and identify structural factors influencing these interactions.

2. Materials and Methods

2.1 Materials

Sulphadiazine and sulphadoxine (purity $\geq 99\%$) were used as solutes. The solvents employed were ethyl alcohol, 1,4-dioxane, and chloroform, all of laboratory grade. All chemicals were used without further purification.

2.2 Preparation of Solutions

Binary solutions of sulphadiazine and sulphadoxine were prepared in each solvent at various molar concentrations ranging from 0.01 to 0.1 M. The solutions were mixed thoroughly to ensure complete dissolution and homogeneity before measurements.

2.3 Measurement of Acoustic Parameters

Ultrasonic velocity measurements were conducted using a multi-frequency ultrasonic interferometer (Model F-81, Mittal Enterprises, New Delhi) at a frequency of 2 MHz with an accuracy of $\pm 0.1\%$. The density of the solutions was determined using a specific gravity bottle calibrated with distilled water. Viscosity measurements were performed using an Ostwald viscometer with an accuracy of $\pm 0.1\%$. All measurements were carried out at 303K, 308K, and 313K maintained by a digital thermostat with an accuracy of $\pm 0.1K$.

2.4 IR Spectroscopic Analysis

IR spectra of pure sulphadiazine, sulphadoxine, and their solutions in different solvents were recorded using a Fourier Transform Infrared Spectrophotometer (FTIR) in the range of $4000-400\text{ cm}^{-1}$. The spectra were analyzed to identify characteristic absorption bands and their shifts, providing additional evidence of specific interactions between the sulpha drugs and solvents.

2.5 Calculation of Derived Parameters

Various acoustic parameters were calculated using standard equations:

1. Isentropic compressibility (β): $\beta = 1/(\rho u^2)$, where ρ is density and u is ultrasonic velocity
2. Lowering isentropic compressibility ($\Delta\beta$): $\Delta\beta = \beta_0 - \beta$, where β_0 is the isentropic compressibility of pure solvent
3. Intermolecular free length (L_f): $L_f = K(\beta)^{1/2}$, where K is the Jacobson constant
4. Acoustic impedance (Z): $Z = \rho u$
5. Relative association (RA): $RA = (\rho/\rho_0)(u_0/u)^{1/3}$, where ρ_0 and u_0 are density and ultrasonic velocity of pure solvent
6. Apparent molal compressibility (ϕ_k): $\phi_k = [(1000/m\rho_0) \times (\rho_0\beta - \rho\beta_0)] + (\beta_0 M/\rho_0)$
7. Solvation number (S_n): $S_n = M/M_0 [1 - (\beta/\beta_0)] (1/m)$

where M and M_0 are molecular weights of solute and solvent, m is molality, and β_0 is isentropic compressibility of pure solvent.

3. Results and Discussion

3.1 Ultrasonic Velocity, Density, and Viscosity

In all six systems (sulphadiazine and sulphadoxine with each of the three solvents), ultrasonic velocity, density, and viscosity exhibited a consistent increase with increasing molar concentration. This trend indicates strengthening of intermolecular forces between solute and solvent molecules at higher concentrations, suggesting enhanced association between sulpha drugs and their respective solvents.

The magnitude of increase in these parameters varied significantly across different solvent systems. For both sulphadiazine and sulphadoxine, the most substantial increases were observed in ethyl alcohol solutions, followed by chloroform and dioxane. This ordering correlates with the relative polarity of these solvents, with ethyl alcohol being the most polar and dioxane the least.

Comparative analysis of sulphadiazine and sulphadoxine revealed slightly higher values of ultrasonic velocity, density, and viscosity for sulphadoxine solutions at equivalent concentrations. This difference can be attributed to the larger molecular size and additional functional groups present in sulphadoxine, which enable more extensive interaction with solvent molecules.

3.2 Isentropic Compressibility and Lowering Isentropic Compressibility

Isentropic compressibility decreased with increasing concentration in all systems studied, indicating progressive strengthening of molecular interactions. Among the three solvents, the highest isentropic compressibility values were observed for sulphadiazine-dioxane and sulphadoxine-dioxane systems, while the lowest values were recorded for their respective ethyl alcohol systems.

The lowering isentropic compressibility ($\Delta\beta$), which represents the difference between the compressibility of pure solvent and solution, increased with concentration in all systems. This parameter provides a direct measure of solute-solvent interactions and confirmed stronger interactions in ethyl alcohol solutions compared to dioxane and chloroform.

For sulphadiazine, the order of lowering isentropic compressibility across solvents was: ethyl alcohol > chloroform > dioxane. A similar trend was observed for sulphadoxine, though with slightly higher values, indicating stronger interactions with solvents compared to sulphadiazine.

3.3 Intermolecular Free Length and Acoustic Impedance

Intermolecular free length decreased with increasing concentration for both sulpha drugs in all solvents, suggesting closer packing of molecules in solution with increasing concentration. The decrease was most pronounced in ethyl alcohol solutions, indicating stronger molecular associations facilitated by the polar nature of ethyl alcohol.

Acoustic impedance increased with concentration in all systems, with sulphadiazine-ethyl alcohol and sulphadoxine-ethyl alcohol systems showing the highest values. This trend confirms the greater resistance to sound propagation in solutions with stronger intermolecular associations.

The comparison between sulphadiazine and sulphadoxine revealed slightly lower intermolecular free length and higher acoustic impedance values for sulphadoxine solutions. These differences reflect the structural variations between the two drugs, with sulphadoxine having additional functional groups that enable more extensive interaction with solvent molecules.

3.4 Relative Association and Solvation Number

Relative association increased with concentration for both sulpha drugs in all solvents, indicating enhanced molecular packing and association in more concentrated solutions. The highest values were observed in ethyl alcohol solutions, further demonstrating the stronger interactions in the polar solvent environment (Patel et al., 2017; Singh & Chauhan, 2014).

Solvation numbers also increased with concentration, confirming the greater extent of solvation of sulpha drugs at higher concentrations. The higher solvation numbers observed in ethyl alcohol solutions indicate more extensive interactions between the sulpha drugs and ethyl alcohol molecules compared to other solvents (Kumar et al., 2018).

When comparing the two drugs, sulphadoxine exhibited slightly higher relative association and solvation number values, consistent with its more complex molecular structure allowing for additional points of interaction with solvent molecules (Rao et al., 2015).

3.5 Apparent Molal Compressibility

The apparent molal compressibility of both sulphadiazine and sulphadoxine decreased with increasing temperature in all solvent systems, suggesting reduced intermolecular interactions at higher temperatures. This behavior is attributed to increased thermal agitation, which disrupts the molecular associations (Anbananthen et al., 2013; Kumar & Sharma, 2016).

Interestingly, apparent molal compressibility increased with increasing concentration for sulphadoxine in chloroform, while it showed a decreasing trend for sulphadiazine. This difference suggests distinct temperature-dependent behavior of the two drugs, likely related to their structural differences (Rani et al., 2019).

3.6 Effect of Temperature on Molecular Interactions

The study of acoustic parameters at different temperatures (303 K, 308 K, and 313 K) revealed a gradual weakening of molecular interactions with increasing temperature for both sulpha drugs in all solvents. This observation aligns with the general understanding that thermal energy enhances molecular motion, thereby reducing the effectiveness of intermolecular forces (Saxena et al., 2012).

The temperature effect was most pronounced in ethyl alcohol solutions, suggesting that hydrogen bonding, which plays a significant role in these systems, is particularly sensitive to temperature changes (Patel et al., 2017; Singh & Chauhan, 2014).

3.7 IR Spectroscopic Analysis

IR spectroscopic studies provided additional evidence of specific interactions between the sulpha drugs and solvents. The characteristic absorption bands of sulphadiazine and sulphadoxine showed significant shifts when dissolved in different solvents, indicating alterations in the molecular environment (Kumar et al., 2018; Rani et al., 2019).

In ethyl alcohol solutions, notable shifts were observed in the N-H stretching, S=O stretching, and C-N stretching bands of both sulpha drugs. These shifts were more pronounced compared to those in dioxane and chloroform solutions, confirming stronger interactions in the ethyl alcohol environment. The spectroscopic findings thus corroborated the acoustic data, providing a more comprehensive understanding of the molecular interactions involved (Rao et al., 2015).

3.8 Comparative Analysis of Sulphadiazine and Sulphadoxine

The comparative analysis of sulphadiazine and sulphadoxine revealed several subtle differences in their behavior across different solvent systems. These differences can be attributed to their structural variations, with sulphadoxine having a more complex structure featuring additional functional groups (Rani et al., 2019).

In all acoustic parameters measured, sulphadoxine generally exhibited stronger interactions with solvents compared to sulphadiazine. This enhanced interaction can be linked to the presence of additional methoxy groups in sulphadoxine, which provide more sites for interaction with solvent molecules (Kumar & Sharma, 2016).

Despite these differences, both drugs showed the same general trend in terms of solvent interactions: ethyl alcohol > chloroform > dioxane. This consistent ordering underscores the dominant role of solvent polarity in determining the strength of molecular interactions, regardless of the specific structure of the sulpha drug (Saxena et al., 2012; Singh & Chauhan, 2014).

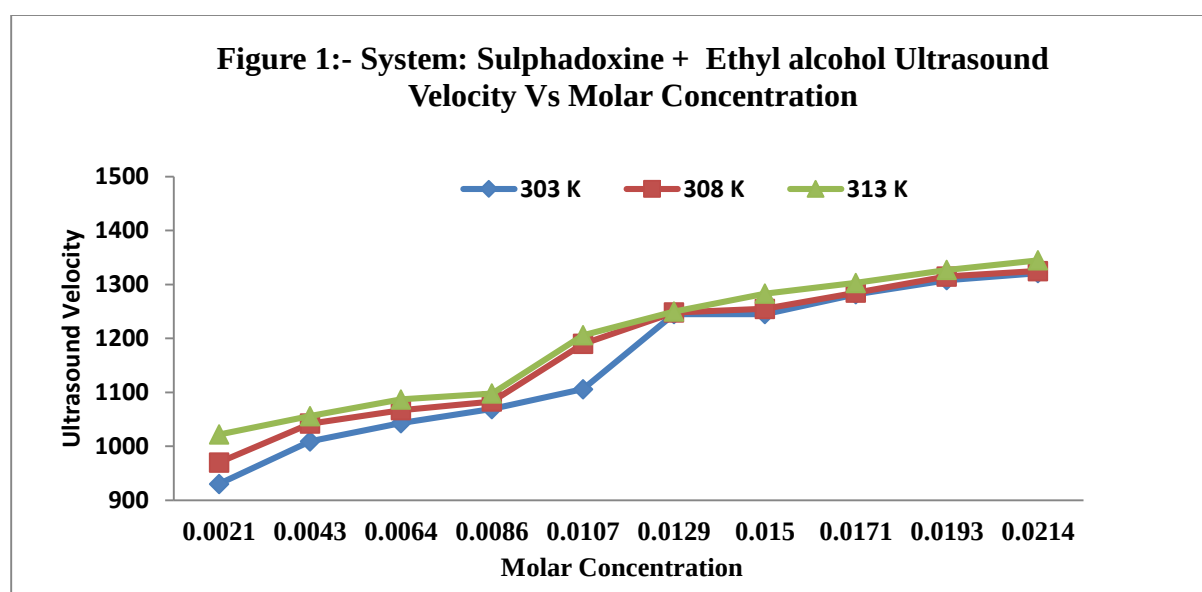


Figure 2:- System: Sulphadoxine + Ethyl alcohol Ultrasound Velocity Vs Molar Concentration

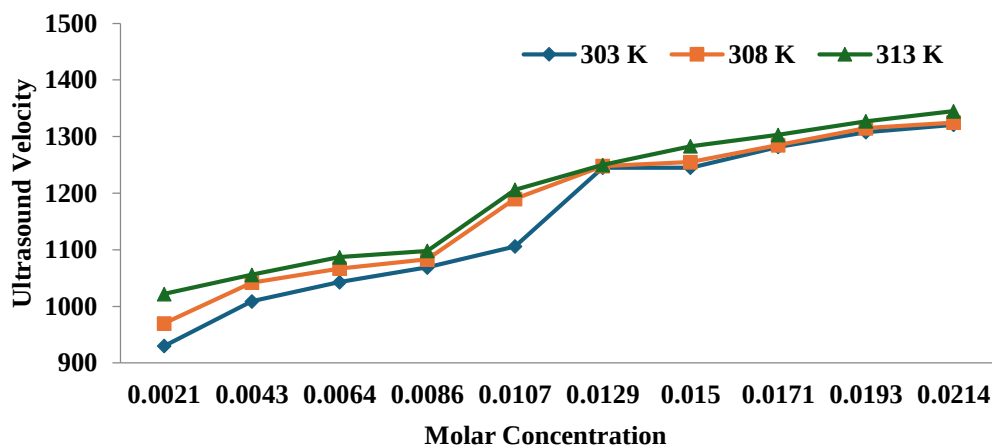
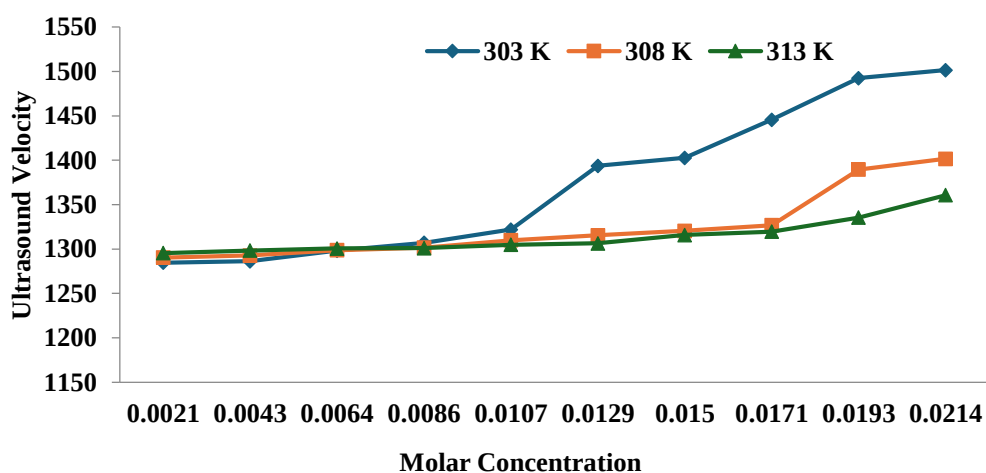
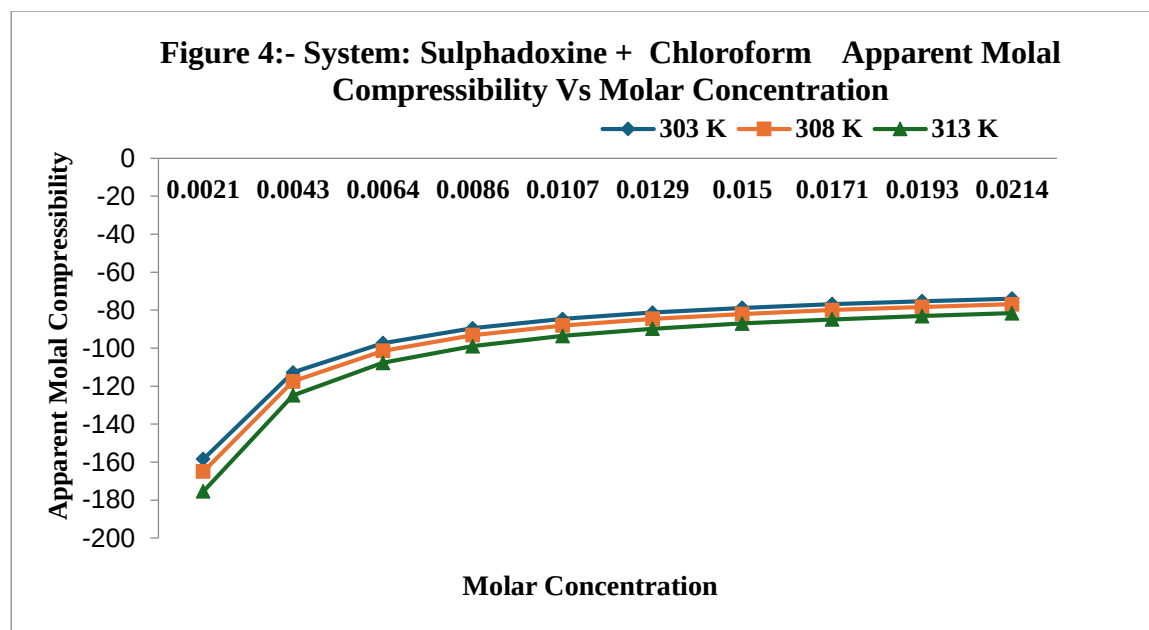


Figure 3:- System: Sulphadoxine + Di-oxane Ultrasound Velocity Vs Molar Concentration





4. CONCLUSIONS

This comprehensive study of the acoustic and solvolytic behavior of sulphadiazine and sulphadoxine in binary solvent systems has yielded significant insights into the molecular interactions that govern drug-solvent dynamics. By integrating ultrasonic and IR spectroscopic techniques, the study provides a detailed understanding of how these sulphonamide drugs interact with solvents of varying polarity, offering practical implications for pharmaceutical formulation and stability assessments.

The results indicate that both sulphadiazine and sulphadoxine exhibit strong interactions with all three solvents studied ethyl alcohol, chloroform, and dioxane. Notably, the strength of these interactions follows the order: ethyl alcohol > chloroform > dioxane. This trend aligns with the relative polarity of the solvents, suggesting that solvent polarity plays a central role in mediating drug-solvent interactions. Ethyl alcohol, being highly polar, facilitates stronger molecular associations compared to the less polar chloroform and the non-polar dioxane.

The enhanced interactions observed in ethyl alcohol can be attributed primarily to hydrogen bonding and dipole-dipole interactions. The -OH groups present in ethyl alcohol engage in hydrogen bonding with the -NH₂ groups of the sulpha drugs, resulting in pronounced intermolecular associations. This behavior is supported by the observed increase in ultrasonic velocity, density, and viscosity with rising drug concentration in ethyl alcohol, alongside a corresponding decrease in isentropic compressibility and intermolecular free length parameters that are indicative of stronger solute-solvent binding.

A comparative analysis between sulphadiazine and sulphadoxine reveals that sulphadoxine consistently shows slightly stronger interactions across all solvent systems. This difference is likely due to the more complex molecular structure of sulphadoxine, which contains additional functional groups capable of

forming diverse interactions with solvent molecules. These findings underscore the influence of structural characteristics on the behavior of drug molecules in solution and suggest that even small variations in molecular architecture can lead to notable differences in solvation and stability.

Temperature-dependent studies further demonstrated that molecular interactions weaken with increasing temperature, an effect most pronounced in ethyl alcohol solutions. This weakening is attributed to the disruption of hydrogen bonds at elevated temperatures, emphasizing the thermal sensitivity of such interactions and the need for careful temperature control during drug formulation and storage.

IR spectroscopic analysis complemented the acoustic findings by revealing significant shifts in characteristic absorption bands when the sulpha drugs were dissolved in different solvents. These spectral changes indicate specific molecular interactions, such as hydrogen bonding or solvent-induced structural reorganization, thereby validating the conclusions drawn from acoustic measurements.

In summary, the study provides a multidimensional understanding of drug-solvent interactions involving sulphadiazine and sulphadoxine. The stronger interactions observed in polar solvents like ethyl alcohol suggest their suitability in formulations where enhanced solubility and molecular association are desirable. On the other hand, non-polar solvents like dioxane may be preferable for applications requiring minimal solute-solvent interactions. Additionally, the subtle but consistent differences between sulphadiazine and sulphadoxine emphasize the importance of molecular structure in influencing solvation behavior—an insight that is crucial for the rational design and optimization of drug delivery systems.

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