SOLUTE-SOLVENT INTERACTIONS OF METHANOL IN AQUEOUS SOLUTIONS OF SULPHONAMIDE DERIVATIVES AT DIFFERENT TEMPERATURES

By

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BSc Chemistry-Geography (NWU), Hons BSc Chemistry (NWU)

Submitted in partial fulfilment of the requirements for the Degree of Master of Science (Chemistry) in the Faculty of Agriculture, Science and Technology

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July 2016

DECLARATION

I hereby declare that the dissertation entitled "Solute-solvent interactions of methanol in aqueous solutions of sulphonamide derivatives at different temperatures" submitted to the Department of Chemistry, North-West University, Mafikeng Campus for the fulfillment of the Master of Science in Chemistry is a faithful record of original research work carried out by me under the guidance and supervision of Dr Indra Bahadur and Prof Eno E Ebenso. No part of this work has been submitted by any other researcher or students. Sources of my information are acknowledged in the reference pages.

Signature..... Date…….

Sinethemba Patricia Manquthu

Signature……. Date……

Dr Indra Bahadur

Signature……..... Date…….....

Prof Eno E Ebenso

DEDICATION

To the late Mirriam Manquthu, my mom. I attribute all my success in life to the moral, intellectual and physical education I received from her.

ACKNOWLEDGEMENTS

I would like to express my heartfelt thanks to my supervisors, **Dr Indra Bahadur** and **Prof Eno E Ebenso** for their boundless support, academic guidance and endless encouragement during each and every step of this project and modelling the manner in which I approach scientific research.

This project would not have been complete without the assistance of a number of people. I would like to thank the North West University (Mafikeng) for giving me the opportunity to do my MSc in Chemistry with them and I am also grateful for the contribution of the Laboratory Technicians within the Department of Chemistry. I would also like to thank Dr G. Varadhi, Dr S. Karlapudi together with the colleagues and members of the Material Science Innovation & Modelling (MaSIM) research group. I am genuinely thankful to the Department of Chemistry, Durban University of Technology, South Africa for providing the facilities to carry out some of the experimental work. I would like to also appreciate the help of the NWU, SASOL INZALO FOUDATION and NRF for funding my studies.

Last but not list, I would like to express my gratitude to my grandmother, Anah Magobe and aunt, Sophy Manquthu, my siblings, extended family and friends. They assisted me to cope through tough times and significantly encouraged me through this work. And finally I would like to thank God for granting me the courage, perseverance and strength to get this far with my studies.

ABSTRACT

The present study examines the effect of temperature and concentration on interactions of methanol in aqueous solutions of sulphonamide derivatives using volumetric and acoustic properties. The following properties namely; densities, ρ, sound velocities, u and viscosities, η, of methanol in aqueous solution of sulphonamide derivatives namely: sulphamethizole, sulphabenzamide, sulphaquinoxaline and sulphachloropyridazine were measured at (293.15 to 333.15) K with 10 K intervals and at pressure p = 0.1 MPa. The data obtained has been used in the calculation of derived properties like apparent molar volumes, V_φ, apparent molar adiabatic compressibilities, k_φ, viscosity B-coefficients and the temperature coefficient, dB/dT. The standard partial molar volumes, V_φ^0, standard partial molar volumes of transfer, ΔV_φ^0, standard partial molar adiabatic compressibility, k_φ^0 and standard partial molar adiabatic compressibility of transfer, Δk_φ^0 were also determined by employing a Redlich-Mayer type equation. These results have been interpreted with respect to the impact of temperature and concentration on interactions, for example (solute-solute), (solvent-solvent) and (solute-solvent) in the studied mixtures. Additional, apparent molar expansivity, E_φ^0, the Hepler's constant values, $\partial^2 V_\varphi^0 / \partial T^2$, and the isobaric thermal expansion coefficient, α_P, were also calculated to substantiate the conclusions drawn from volumetric and acoustic properties. Consequently, the outcomes from these study can be utilized in flow affirmation and oil recovery, configuration of partition techniques, determination of solvent and emanation, drug design, understanding the pharmacokinetics and pharmacodynamics of sulphonamides and estimation of the dispersion of chemicals in different various ecosystems.

Keywords: Sulphonamide, Methanol, Apparent molar adiabatic compressibility, Apparent molar volume, Redlich-Mayer type equation.

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LIST OF ABBREVIATIONS, SYMBOLS AND NOTATIONS

QSAR	Quantitative structure activity relationship
QSPR	Quantitative structure–property relationship
QM	Quantum mechanics
IKBI	Inverse Kirkwood–Buff integrals
EHSA	Applied the Extended Hildebrand solubility approach
UV	Ultraviolet
ACF	Activated carbon fiber
HOMO	Highest occupied molecular orbital
MLR	Multiple linear regression
DHPS	Dihydropteroate synthetase

ρ	Density
u	Sound velocity
η	Viscosity
T	Temperature
m	Molality
M	Molar mass

V_φ	Apparent molar volume
k_φ	Apparent adiabatic compressibility
ρ and ρ_0	Densities
$k_{s\,0}$ and k_s	Coefficient of adiabatic compressibility of reference solvent
V_φ^0	Limiting value apparent molar volume
k_φ^0	Limiting value apparent molar adiabatic compressibility
S_v, B_v, S_k and B_k	Represent the values of the experimental slopes
ΔV_φ^0	Partial molar volumes of transfer
Δk_φ^0	Partial molar adiabatic compressibility of transfer
α_p	Isobaric thermal expansion coefficient
E_φ^0	The limiting apparent molar expansibility
$\partial^2 V_\varphi^0 / \partial T^2$	Hepler's constant

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CHAPTER 1

INTRODUCTION

The physicochemical properties for instance densities (ρ), sound velocities (u), and viscosities (η), of liquid and liquid mixtures are utilized to recognize the manner at which molecular interactions and its tendency of structure making or breaking impacts in the binary system. These properties can extend the series of structural properties and the possibility of the molecular interactions among the solvent molecules [1].

Sulphonamides are part of a distinctive class of compounds which form a minimum of five different classes of pharmacologically dynamic agents [2]. They are organic sulphur compounds containing the radical $-SO_2NH_2$ which is the amide of sulphonic acid and acts such as an antimicrobial agent through the inhibition of bacterial growth [3]. Sulphonamide derivatives are well-known inhibitors of carbonic anhydrase [4, 5]. Sulpha drugs result from sulphonamides, although all sulphonamides are not sulpha drugs. The term sulpha drugs is merely used for clinically used antibacterial agents that are structurally derived from 4-aminobenzenesulphonamide, in which the sulphonamide nitrogen is substituted [6]. Since their introduction, sulpha drugs have been used as protease inhibitors [7-19], anti-inflammatory [11], antiviral and anticancer agents [12].

These drugs are mostly used for the treatment of infections that are triggered by Gram positive and Gram negative microorganisms [13]. Aliphatic sulphonamides derivatives possess the highest influential antibacterial activity for Gram negative than Gram positive bacteria and antibacterial activity declines with the increase in length of the carbon chain [14]. These compounds have displayed noticeable inhibitory activity against Gram-positive bacteria [15].

It is well understood that sulphonamides can demonstrate a variety of pharmacological activities like as anti-diabetic, antibacterial and antitumor actions through the interactions of different functional groups with no alteration of the structural SO_2NH feature [16-19]. Sulpha drugs are a vital class of pharmaceutical composites that show a wide range spectrum of biological activities [20]. Above 30 drugs carrying this functionality are used clinical as well as antibacterials, hypoglycemics, diuretics, anticonvulsants and HIV protease inhibitors [21]. Sulphonamide derivatives of azo dyes succeed to improve light stability, water solubility and fibre fixation [22].

Sulphonamides are the main functional portion of numerous structures of drugs because of their stability and tolerance in humans [23, 24]. These compounds exert their antibacterial action through the competitive inhibition of the enzyme dihydropterase synthetase to the substrate *p*-aminobenzoate [25]. There are several chemotherapeutically important of these drugs such as sulphaacetamide; sulphamerazine and sulphadimidine have the SO_2NH moiety which is an essential toxophoric function [26]. Those sulphonamides that are heteroaromatic or aromatic are accountable for the obstruction of the development of tumour cells [27].

1.1. History of sulphonamides

Gerhard Domagk discovered that 4'-sulphamyl-2,4-diaminoazo-benzene, which was later called prontosil (**Figure 1.1**) had a high antibacterial activity and this lead to the development of several sulphonamides through its metabolite sulphanilamide [28]. In 1935 he published the results of his research work demonstrating that prontosil had the ability to cure staphylococcal infections in mice and rabbits [29]. Sulphonamides were the first effective chemotherapeutic agents employed systematically for the inhibition and cure of bacterial infections in human beings [30].

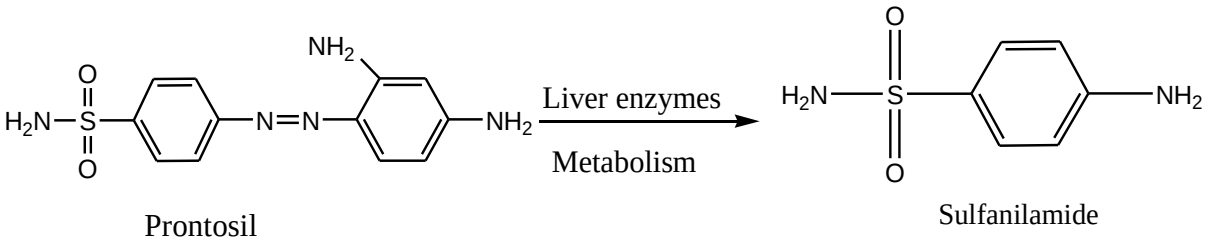


Figure 1.1: Structural formulas of prontosil with its metabolite (sulphanilamide) within the human body.

In 1939 a Nobel Prize in medicine was awarded to Domagk for his definitive discovery which was later on in 1940 referred to as the only identified chemicals having the ability to cure serious bacterial infections in humans in doses permitting an acceptable margin of safety [31]. This discovery speedily resulted in the growth of a range of sulpha drugs, all of which were essentially substituted sulphanilamides [32].

The enormous interest in these drugs clinically is based on the numerous derivatives that can be synthesised, from a microbiologic point of view all of them are identical but vary in pharmacokinetical characteristics [33].

After sulphanilamide discovery, thousands of chemical variations were studied. The best therapeutic results were obtained from compounds in which one hydrogen atom of the SO_2NH_2 group was replaced by a heterocyclic ring [34]. Sulphonamide derivatives are amide derivatives of sulphonic acid since they are produced by introduction of an amino group in sulphonic acid replacing its hydroxyl group [35]. These compounds have a general structure denoted by **Figure 1.2**.

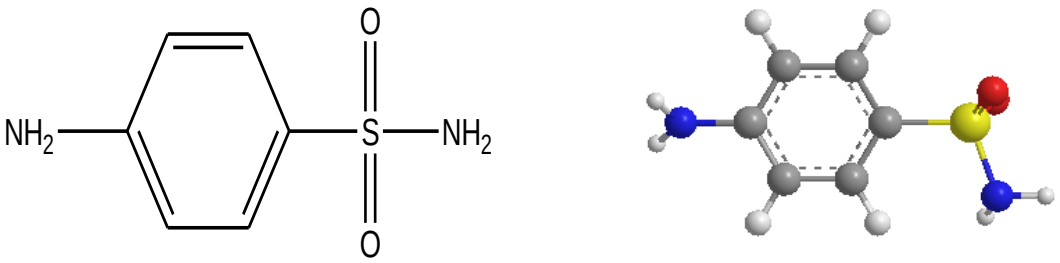


Figure 1.2: The general structure of sulphonamides.

Sulphonamides are as well not active if *p*-amino group is acylated, benzene is substituted or when the SO_2NH group not attached right onto the benzene ring [36]. The lipophilicity of the N1 group has the main effect on protein binding and the more lipids are soluble is the more of the sulphonamide will be protein bounded [37]. The aniline (N4) amino group is of great importance for activity because any change of it beside to create pro-drugs results in a loss of activity, meaning the SO_2NH moiety will lose its biological importance [38]. The syntheses of these drugs have led to the discovery of new compounds with varying pharmacological characteristics in this main structure R; R1 could possibly be hydrogen, alkyl, aryl or hetero aryl [36].

1.2. Preparation methods of sulphonamides

The majority of sulphonamides are prepared via the reaction of a sulphonyl chloride with ammonia or primary /secondary amines or through related transformations [39, 40]. Given the severity of these reaction conditions, sulphonyl chlorides are barely introduced into the improved intermediate through C–S bond formation. As a result the variety of sulphonamide functionality is in fact limited and cannot be readily differentiated at both sulphur and nitrogen in the last step of the formation of a large ensemble of compounds [41].

Normally, sulphonamides are prepared through the reaction of a sulphonyl chloride with ammonia or primary or secondary amines [42]. Though, these sulphonyl chlorides have certain disadvantages like when they are mishandled easily and are not convenient for long-period storage [43]. During the solvation of sulpha drugs in basic organic solvents their acidic properties become sufficiently improved to permit direct titration with a strong base [44].

So far various synthetic methods have been described. Some of the current and common methods are demonstrated concisely below and are given through sulphonyl chloride or by the aid of transition metals by way of Grignard reagents or catalyst [45]. From **Figure 1.3 to Figure 1.9** given below are different schematics showing the preparation reaction of sulphonamides.

1.2.1. Sulphonamides preparation from thiols by sulphonyl chloride

Currently direct oxidative conversion of thiols to sulphonamides with H_2O_2-$SOCl_2$ (**Figure 1.3**) has been reported by Bahrami et al. [46] where the reaction with amines and corresponding sulphonamides are obtained in good yields within a short time of reaction [47].

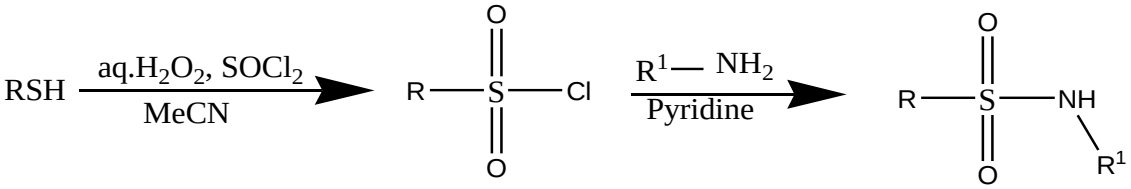


Figure 1.3: Transformation of thiols into sulphonamides using H_2O_2-$SOCl_2$.

Sulpha drugs were easily prepared with high yields obtained when aryl thiols having either electron-withdrawing or electron-donating substituents [48]. A method of preparation of these drugs from thiols was described by Wright *et al.* [49], demanding *in situ* production of a sulphonyl chloride with the aid of sodium hypochlorite (commercial bleach) facilitated the

oxidation of thiol. The residue sulphonyl chlorides were then confined with benzylamine in the following reaction to create sulphonamides with a yield of 98% (**Figure 1.4**).

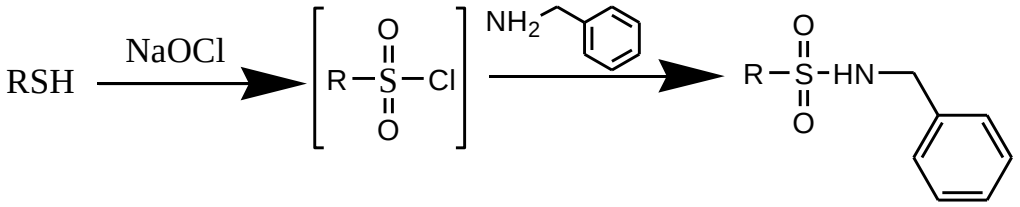


Figure 1.4: Sodium hypochlorite as facilitated oxidation of thiols.

1.2.2. Preparation of sulphonamides from sulphonic acid

Beginning from sulphonic acid, sulphonyl chloride emerges as an intermediate. This synthesis is done under microwave irradiation, it has revealed a good functional group tolerance and high yields [50] (**Figure 1.5**).

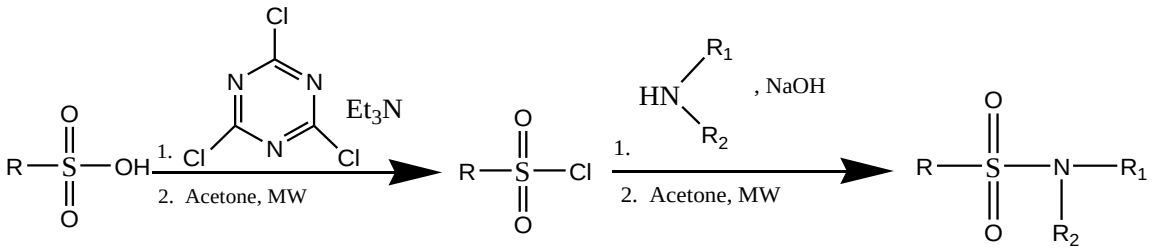


Figure 1.5: Preparation of sulphonamides by means of microwave irradiation.

This reaction was conducted in standard heating delivered equivalent sulphonamide leading to good yields [51]. Chavasir *et al.* [52] described the novel using of trichloroacetonitriletriphenylphosphine complex (Cl3CCN/PPh3) for sulphonamide construction. One of the notable advantages of this methodology is that it is not limited to aromatic sulphonyl chlorides, it can also be applied to heterocyclic and aliphatic sulphonyl chlorides (**Figure 1.6**).

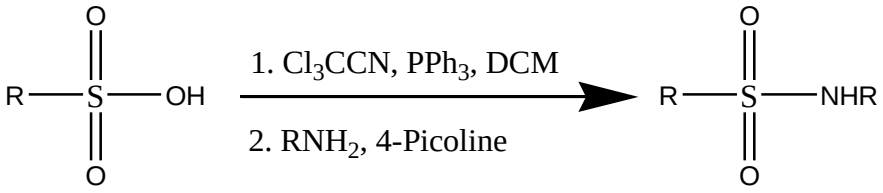


Figure 1.6: Preparation of sulphonamides with trichloroacetonitriletriphenylphosphine complex.

1.2.3. Sulphonamides from sulphenamides

Another inventive way of sulphonamides preparation was demonstrated in the production of 2-amino-9H-purin-6-sulphonamide. Mild and selective oxidants were used by Revankar *et al.* [53]. They discovered that the oxidation of 2-amino-9H-purin-6-sulphenamide utilising one equivalent of *m*-CPBA result in 48% of the yield (**Figure 1.7**).

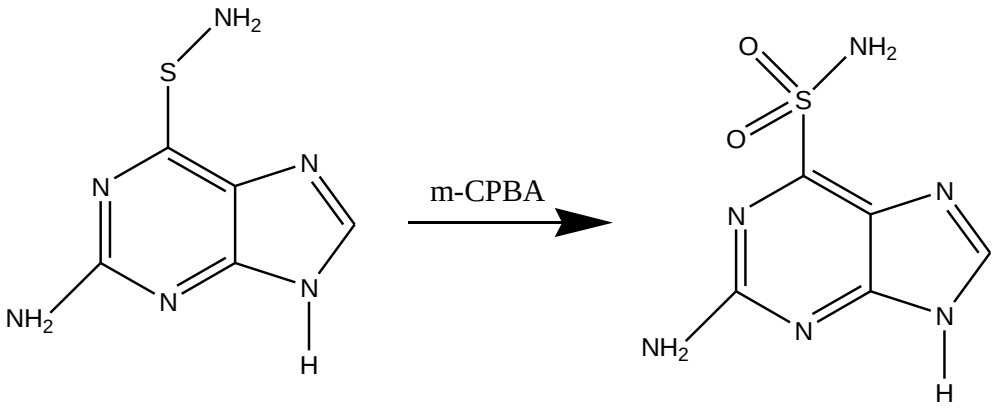
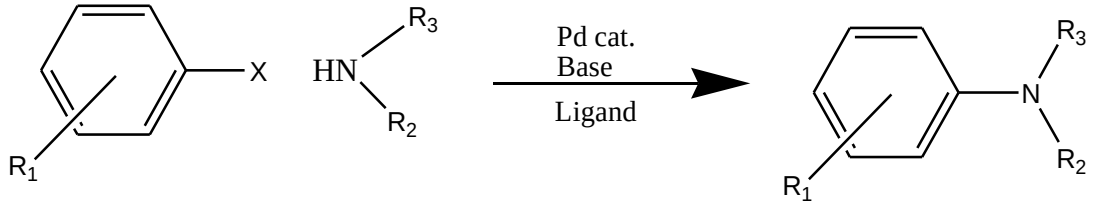


Figure 1.7: The Oxidation of sulphonamides with using *m*-CPBA.

1.2.4. Sulphonamides preparation by means of using transition metal catalyst

Transition metal catalyzed cross-coupling C‑N bond creation has been studied broadly, in which the most well understood palladium catalyzed *N*-arylation is the Buchwald-Hartwig reaction [54] given in **Figure 1.8**.



X= Cl, Br, OTf
R_2= Alkyl, Aryl, H
R_3= Alkyl, Aryl

Figure 1.8: Buchwald-Hartwig reaction for sulphonamide synthesis.

Lately, Guo *et al.* [55] have prepared a variety of sulphonamides using copper (I) catalysed coupling and aryl bromide/ iodide (**Figure 1.9**). In the course of the optimization process, they discovered that using an amino acid as a ligand presents several advantages for instance easy removal after the reaction. After studying a number of amino acids, they learned that N, N-dimethylglycine and N-methylglycine are the best effective with Cu (I). Together with DMF as the solvent and K_3PO_4 as the base, all anticipated *N*-arylsulphonamides can be synthesised up to 99% yield.

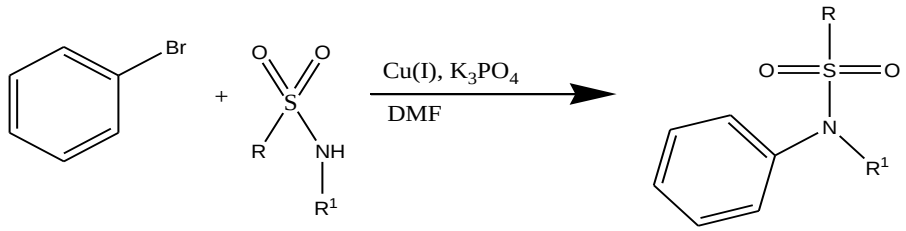


Figure 1.9: Synthesis of *N*-arylsulphonamides using Cu(I).

1.3. Applications and uses of sulphonamides

The discovery of sulphonamides as antibacterial agents during the early 30s became the starting of the most interesting era of chemotherapeutic agents [56]. Sulphonamides were the first class of antibiotics introduced in the 1930s and continue to be important due to their safety, effectiveness and low cost although adverse effects are common [57]. The sulphonamide that was first clinically used was prontosil [58].

Advanced studies revealed that modified sulphonamides showing high to moderate antibacterial activity [59]. Lately sulpha drugs have been found to be effective cysteine protease inhibitors and this could perhaps prolong their therapeutic applications to include diseases like Alzheimer's, cancer and arthritis [60]. Until now more than twenty thousand derivatives of sulphanilamide have been produced [61].

The sulphonamides (sulpha drugs) are mostly used during the treatment of eye, urinary tract, mucous membranes and gut infections [62]. The antibacterial sulphonamides carry on playing a vital role in chemotherapy single-handedly or within a combination with other drugs [63]. They have the ability to work as a peptide surrogates with distinctive physical properties and this have made sulphonamide(s) an ideal functional group in the development of novel non-peptide matrix metalloproteinase inhibitors [64]. Perfluorinated alkyl sulphonamides are utilised in a wide range of consumer products such water and oil resistance together with surface treatments for fabric, in fire-fighting foams, carpet, paper, leather, upholstery and as insecticides [65]. Sulphonamides are used as antibiotics in veterinary medicines for treatment infections on livestock [66, 67].

1.4. Significance of the study

The significance of sulphonamides in medicinal chemistry cannot be ignored because it establishes an essential class of drugs that are used extensively as pharmaceutical and agricultural agents [68]. Sulphonamides are bacteriostatic drugs; they inhibit DNA synthesis and stop cell division [69]. Studies have shown that some sulphonamide derivatives are used as antibacterial [70], antifungal [71] and antiviral agents [72]. They are all given orally except sulphanilamide that consists of sodium salts, which are used for intramuscular or intravenous injections [73, 74].

There seems to be no sufficient information on proposed mechanism for the electron transfer process between sulphonamides and immiscible liquid phases, aqueous media and biological membrane models [75]. The understanding of structural conformation of sulphonamides is vital for drug design, since the sulphonamide group is an important functional group and determines their biological activity [76].

Also little work has been reported on molecular interactions of aqueous solutions of sulphonamide derivatives. Therefore, in the present study the determination of viscosity, density and sound velocity of aqueous sulphonamide derivatives is conducted in order to understand the structural properties and solute-solvent interactions. Thermo-physical and thermodynamic properties will furthermore provide information about the intermolecular interactions [77, 78] and allows for the development of new correlations and thermodynamic predictive models [79].

The structural arrangements and molecular interactions happening at molecular level in the binary mixtures can be comprehended by the analysis of their physical properties such as

dielectric constant, density, viscosity and refractive index [80]. Water is the notable polar solvent with a structure which is determined to an immense extent by the bonding between molecules. On the other hand, surely understood protic solvents are the alcohols which have one acidic hydrogen molecule on the -OH group [81, 82]. At the point when working with polar fluids, this property can give much valuable information about the nearby structure because of the orientation of the molecules and to interactions between adjacent units [83].

The physical properties of water and aqueous mixtures of organic solvents are essential for many reasons; particularly mixing volume and viscosity effects have theoretical and practical importance but strong deviations from linearity are often experienced in aqueous liquid mixtures [84]. Although thermodynamic properties of binary liquid mixtures with associated component have been studied extensively, limited studies have been done on sulphonamides [85].

Drug-macromolecular interactions are a vital occurrence in physiological media, for example blood and membranes. One of the very much perceived approaches to the study of molecular interactions in fluids is through usage of thermodynamic methods; thermodynamic properties are mostly the helpful parameters for interpreting solute-solute and solute-solvent interactions in the solution phase [86].

The knowledge of solubility of sulphonamides (sulpha drugs) at different temperature is vital for physical stability studies of liquid dosage forms, in processes where temperature changes are involved and in the preformulation phase of a new drug where small quantity of the drug is present [87]. Characterization of properties of the molecules in pharmaceutical solvents assists in finding out correlations between the structure and topology of the molecules with respect to

their partitioning, solubility and solvation properties [88]. Hence it is important to study the thermodynamics properties of sulphonamides.

Furthermore, the preferential solvation of the solute using solvent components in the mixtures offers a potent tool for understanding the molecular interactions taking place in dissolution processes of the drug [89]. Also the solubility of active ingredients is a fundamental property to be considered because it affects numerous biopharmaceutical and pharmacokinetic characteristics [90, 91].

Co-solvency as a solubilizing method has been extensively used in pharmaceutical dosage outline; nevertheless it has been lately that the mechanisms participating during modification of drug solubility began to be approached from a thermodynamic point of view, together with the valuation of the preferential solvation of a solute using solvents in the mixtures [92, 93].

In addition, the experimental drug performance in co-solvent mixtures is regularly evaluated as a function of temperature and composition for the purification of crude materials, preformulation analyses and understanding of the molecular mechanisms taking part in the chemical and physical stability of pharmaceutical dissolutions [94].

Though several semi-empirical and theoretical models can be implemented to predict drug solubilities in solvent mixtures, the availability of experimental data is still crucial for pharmaceutical scientists [95] due to the solubility of sulphonamides in neat water being too small [96, 97].

This may result in improved evaluation of the physiological distribution of drug molecules and offer an enhanced understanding of biopharmaceutical properties of drugs [98]. Accurate measurements of volumes and viscosities over the entire composition range are essential to understand the nature of interactions between water and nonpolar groups, the alleged hydrophobic solvation [99].

It is acknowledged that the thermo-physical properties of liquid systems are definitely linked to the molecular interactions present in different binary liquid mixtures [100]. Binary mixtures of water with alcohols are important in numerous engineering application [101].The area of preferential solvation of sulpha drugs has been reported by Delgado *et al.* [102], Jiménez *et al.* [103] and others, thus it is of great importance to conduct thermodynamic studies of sulphonamides. Thermo-physical data are useful industrially because they contribute in the optimization of design in several industrial processes [104- 106].

In the industry of chemicals, information about density and viscosity of liquid mixtures and their reliance with composition and temperature is imperative in various applications for surface facilities, mass transfer operations and pipeline frameworks [107]. Measurement of the sound velocity in liquids is a potent source of information (like the effects of small concentrations changes) about the thermo-physical properties of chemical substances as well as their mixtures [108].

Thermodynamic properties of multicomponent liquid mixtures and their investigation as far as interpretive models establish an extremely captivating subject [107]. The characterization of mixtures via their thermodynamic and transport properties is critical from the major perspective of comprehend their mixing behaviour [109-114]. An in-depth knowledge of transport

properties of non-aqueous solutions is fundamental in numerous chemical and industrial applications [115]. Properties for instance density and viscosity at numerous temperatures both for pure chemicals and their binary liquid mixtures over the entire composition series are helpful for comprehension of the thermodynamic and transport properties related with fluid flow and heat [112, 116].

Excess molar volumes and partial molar volumes can assist in the basis for understanding certain molecular interactions (for example hydrogen-bonding interactions, dispersion forces) in binary mixtures [117]. Excess molar volume data is useful in the designing of technological processes reactions [118] and can be utilised in the prediction of vapour liquid equilibria using suitable equation of state models [119].

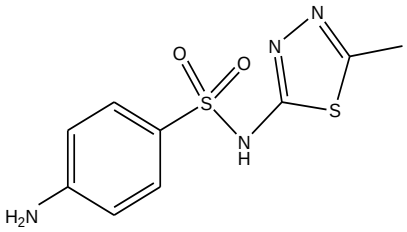
A vital hypothesis in the traditional drug design model is that the impact of the drug inside the human body is a result of the molecular recognition between the drug and the target. The pharmacological activity of the drug at its location of action is eventually a result of the electronic nature and spatial arrangement of its atoms together with manner of interaction these atoms have with the biological counterpart [120]. Computational chemistry assists with the characterization of the dynamics, structure and energetics of these interactions [121]. For example, molecular mechanics based methods can efficiently help to discover new drugs and these computationally low-cost methods are regularly used currently during drug design [122, 123].

The functionally important molecules and physicochemical interactions of a drug in a living organism [124] might consist of hydrogen bonding, covalent, ionic, ion−dipole interactions, charge transfer or hydrophobic hydration [125] and are of pronounced assistance for understanding the pharmacokinetics and pharmacodynamics [126] of drugs. These interactions are tremendously convenient for the transformation and migration of drugs or their metabolites that go into water through fecal excretions, urine and so forth [127] and pollute water. Since most of the biochemical processes transpire in aqueous media, the studies on the physicochemical interactions in the aqueous phase using volumetric and ultrasonic methods offer valuable information in medicinal and pharmaceutical chemistry [128]. The drug-water molecular interactions and their dependence on temperature play a vital part in understanding of drug action on the molecular level [129, 130].

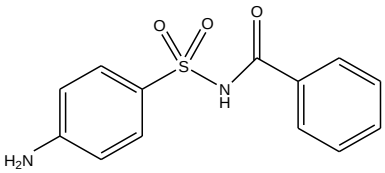
To the best of our knowledge, no work has been accounted for in open literature for the considered systems. The significance of these compounds as agricultural and pharmaceutical agents has prominently stirred the requirement for broad information on their thermo-physical and thermodynamic properties together with their aqueous mixtures in organic solvents.

Hence, in the present work we present new comprehensive investigation of the density, ρ, sound velocity, *u*, viscosity, *η*, and refractive index, *n*, of methanol in aqueous solutions of sulphamethizole, sulphabenzamide, sulphaquinoxaline and sulphachloropyridazine at (293.15 to 333.15) K and at pressure p = 0.1 MPa. The solute-solvent interactions in the mixtures were evaluated by means of partial molar properties, and apparent molar adiabatic compressibility, k_φ, and apparent molar volume, V_φ, were calculated. The standard partial molar adiabatic compressibility, k_φ^0, and standard partial molar volumes, V_φ^0, were determined using the Redlich-Mayer type equation and transfer parameters such as Δk_φ^0 and ΔV_φ^0 have been

evaluated too the apparent molar expansivity, E_{φ}^{0}, isobaric thermal expansion coefficients, α_p, and the Hepler's constant, $\partial^2 V_{\varphi}^{0} / \partial T^2$, values reported in this study to contribute in the conclusions attained from acoustic and volumetric properties. The structures of the studied sulphonamide derivatives are shown in **Figure 1.10** below.



(a)



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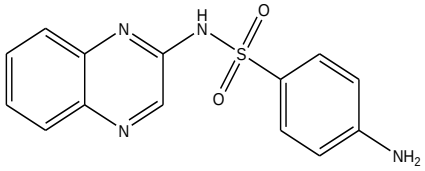

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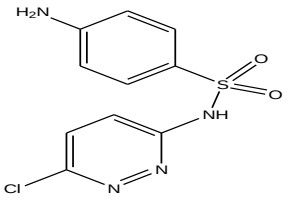


(d)

Figure 1.10: Chemical structure of **(a)** Sulphamethizole, **(b)** Sulphabenzamide, **(c)** Sulphaquinoxaline and **(d)** Sulphachloropydizine.

1.5. RESEARCH AIM AND OBJECTIVES

Aim

The purpose of the proposed research is to carry out an extensive investigation of thermo-physical and thermodynamics properties of four selected sulphonamide derivatives: sulphamethizole, sulphabenzamide, sulphaquinoxaline and sulphachloropydizine with methanol.

Objectives

- To measure the thermo-physical properties such as density, sound velocity and viscosity of sulphonamide derivatives and their binary mixture at various temperatures.
- To investigate the effect of temperature and concentration on these properties and their derived properties.
- To investigate the effect of different sulphonamide derivatives on intermolecular interaction.
- To investigate the solute act as structure maker or breaker in solution.
- To investigate the types of interactions such as solute-solute, solute-solvent and solvent-solvent.

CHAPTER 2

LITERATURE REVIEW

Delgado *et al.* [131] conducted study on the preferential solvation of sulphadiazine, sulphamerazine and sulphamethazine in ethanol and water solvent mixtures conferring to the Inverse Kirkwood–Buff Integrals (IKBI) method. It was found that the sulphonamides were sensitive to solvation effects and the preferential solvation parameter by ethanol was found to be negative in water and ethanol rich mixtures.

Jiménez *et al.* [132] evaluated the solubility temperature dependence and preferential solvation of sulphadiazine in 1, 4-dioxane+ water co-solvent mixtures. The preferential solvation of the drug by both solvents was analysed using the IKBI and it was found that the drug was preferentially solvated by water in mixtures rich in water and 1,4-dioxane but preferentially solvated by 1,4-dioxane in the ones with intermediate compositions.

Martinez *et al.* [133] did a thermodynamic study of the solubility of some sulphonamides in octanol, water and the mutually saturated solvents. The solubility of the sulphonamides was determined on the ionic strength and isoelectric point. And the solubility data obtained at 25 to 40°C was used to evaluate the enthalpy, entropy and free energy of the solution. The activity coefficients in aqueous media were found to be greater than in the organic one, which resulted in the interactions between sulphonamides and water to be weak. For the mixtures of octanol and sulphonamides it was more complicated to propose the degree of interaction due to the solvent–solvent energies being small and solvent–solute interaction energies were small or large.

Delgado *et al.* [134] performed solubility and preferential solvation study of sulphadiazine in methanol and water mixtures at several temperatures. A non-linear entropy-enthalpy relationship was observed for sulphadiazine in the plot of enthalpy against Gibbs energy of mixing and the IKBI was used to analyse the preferential solvation of the drug.

Delgado *et al.* [135] worked on the preferential solvation of some sulphonamides in 1,4-dioxane + water co-solvent mixtures at 298.15 K agreeing with the IKBI method. It was discovered that all the sulphonamides in the study were very sensitive to solvation effects so the preferential solvation parameter was found to be negative in 1,4-dioxane-rich and water-rich mixtures however positive in the intermediate co-solvent compositions. The molecular reasons for the results obtained were not clear particularly the complexity of these compounds with several acidic and basic sites and it was not easy to propose the relevant molecular interactions that were involved.

Delgado *et al.* [136] worked on the preferential solvation of some structurally related sulphonamides in 1-propanol and water co-solvent mixtures. The sulphonamides were found to be preferentially solvated by 1-propanol in mixtures containing compositions but preferentially solvated by water in1-propanol-rich and water-rich mixtures at all temperatures that were considered

Şanli *et al.* [137] conducted a study consisting of determination of dissociation constants, pKa values of some sulphonamides by using the reversed-phase liquid chromatographic data in acetonitrile-water binary mixtures. Linear relationships were observed on the plot of calculated pKa values of sulphonamides in different solvent mixtures against the molar fraction of

acetonitrile. The pKa values of sulphonamides were found to have been influenced by the percentages of organic solvent that was added to the solutions.

Raevsky *et al.* [138] did an extensive analysis on the octanol-water partition coefficients of sulphonamides then experimentally determined and calculated the partition coefficients using physicochemical descriptors. Direct correlation with molecular polarizability and H-bond acceptor ability approaches were applied in the calculation of partition coefficient values. And both the used methods ensured satisfactory estimation of octanol-water partition coefficients.

Delgado *et al.* [139] determined the preferential solvation of some sulphonamides in propylene glycol + water solvent mixtures according to the IKBI and Quasi-Lattice Quasi-Chemical methods. IKBI was applied to equilibrium solubility values of the drugs in propylene glycol + water mixtures. The drugs were found to be preferentially solvated by water in water-rich mixtures however they were solvated by propylene glycol in all the other mixtures were at all temperatures measured.

Delgado *et al.* [140] executed study on the solution thermodynamics and preferential solvation of sulphamerazine in methanol and water mixtures. A non-linear entropy-enthalpy compensation was discovered for sulphamerazine in the methanol and water mixtures. The dissolution process of the drug was found to be entropy driven when coming to water-rich mixtures but was enthalpy driven in other mixtures. It was suggested that hydrophobic hydration took part in the drug's solvation in water-rich mixtures.

Meler *et al.* [141] did an evaluation on preparations pharmaceutical salazosulphapiridin relying on used food supplements containing chitosan in model "in vitro". An assumption was made

that antagonistic interaction occurred between the analysed drug and the polymer which consists in the absorption of the drug on a polymer.

Pal *et al.* [142] reported the volumetric properties of glycine in aqueous solutions of some sulpha drugs at different temperatures. The values of limiting partial molar volumes of glycine in aqueous drug solutions were found to be positive this served as an indication of the presence of strong solute-solvent interactions. The interactions were found to be directly proportional to the concentration of the sulpha drugs excluding with sulphanilic acid.

Banipal *et al.* [143] evaluated the volumetric and viscometric properties of some sulpha drugs in aqueous solutions of NaCl at temperatures ranging from 288.15 to 318.15K.
The partial molar volumes and viscosity were measured from density and flow time measurements sulpha drugs in water and aqueous solutions. The obtained results of activation free energy for the viscous flow of solutions suggested that the establishment of transition state was less favoured in the presence of investigated sulpha drugs.

Banipal *et al.* [144] conducted a volumetric and viscometric study on the interactions occurring between sulpha drugs and magnesium chloride in aqueous solutions at different temperatures. The densities and viscosities were measured for sulphanilic acid, sulphanilamide and sulphosalicylic acid dihydrate in aqueous magnesium chloride solutions at temperature ranging from 288.15 to 318.15 K and the results indicated that the solubility of the drugs was greater in aqueous solutions of magnesium chloride than that of sodium chloride. Sulphanilamide and sulphanilic acid had negative values of excess molecular volume this suggested that there was self-association within these two drug compounds in this system.

Perlovich conducted a study on the thermodynamic approaches to the challenges of solubility in drug discovery and their development using some sulphonamides [145]. It was concluded that using thermodynamic characteristics of sublimation, dissolution, solvation and distribution can extend the knowledge and understanding of drug delivery processes and make a substantial impact to developing the logical technique of structural optimization of molecule properties.

Ashraf-Khorassani *et al.* [146] evaluated the solubility of sulphamethazine and sulphadimethoxine in supercritical carbon dioxide, fluoroform, and also in subcritical Freon 134A. Results showed that sulphamethazine and sulphadimethoxine have higher solubility in subcritical Freon 134A than in CO_2 and supercritical fluoroform

Zhang *et al.* [147] determined the solubilities of sulphadimethoxine, sulphamethazine, sulphamethoxydiazine, sulphamethoxazole, sulphamonomethoxine and sulphaquinoxaline in 1-octanol at temperatures ranging from 298.15 to 333.15K. With the aid of the static equilibrium method the solubilities of the drugs were experimentally determined in 1-octanol from at different temperatures. The data was correlated with the modified Apelblat equation.

El-Wahed *et al.* [148] did a spectroscopic, thermal and biological study of coordination compounds of sulphasalazine in Cr(III), VO(II) Mn(II), Hg(II), ZrO(II), and Y(III) transition metal complexes. The complexes were acquired and characterized by spectroscopic and physicochemical methods. The IR spectra of the complexes suggested that sulphasalazine acts as a mono-anionic bidentate ligand. The thermal decomposition of the complexes and thermodynamic parameters were predicted via the Coats–Redfern and Horowitz–Metzger equations and vitro antimicrobial activities of the sulphasalazine and the complexes were tested.

Sadeghi *et al.* [149] conducted a study on the solid phase extraction by means of silica gel functionalized with sulphasalazine (SiCPMS-SSZ) for preconcentration of U(VI) ions from water samples. The results revealed the high potential of SiCPMS-SSZ for U(VI) separation from co-existing alkaline, alkaline earth, transition and heavy metal ions and the competence of the new sorbent in retrieval of U(VI) ions at various concentrations in water samples was evaluated.

Bani-Yaseen conducted an extensive analysis on the solvatochromic and fluorescence behaviour of sulphisoxazole [150]. Results demonstrated that photo-physical properties of sulphisoxazole and steady state fluorescence emission are both solvent dependent. The reported findings in the study could be used in obtaining conclusive knowledge regarding the pharmacokinetics of sulphisoxazole.

Delgado *et al.* [151] did a thermodynamic study on the solubility determination of sulphapyridine in some ethanol + water mixtures and the Gibbs energy, enthalpy, and entropy of solution were obtained by using the Van't Hoff and Gibbs equations from these solubility data. The solubility was high in the mixture with ethanol and very low in pure water at all measured temperatures and a non-linear entropy-enthalpy relationship was witnessed on the plot of enthalpy versus Gibbs energy of solution. It was concluded that the solvation of sulphapyridine in ethanol + water mixtures depends mostly on the composition of the solvent.

Ortyl *et al.* [152] determined the refractive index modulation in the polyurethane films containing diazo sulphonamide chromophores. It was discovered that the refractive index changes under illumination depending on the content of chromophore.

Delgado *et al.* [153] conducted a study on the solution thermodynamics of sulphadiazine in some ethanol + water mixtures and the calorimetric values related to a drug fusion process were used to calculate the thermodynamic quantities of mixing. Entropy was found to be the driving mechanism for sulphadiazine solubility in ethanol-rich and water-rich mixtures.

Delgado *et al.* [154] evaluated the solubility of sulphapyridine in propylene glycol + water mixtures in correlation with the Jouyban–Acree model, this model was also used to calculate the generated solubility data. It was discovered that the driving mechanism for sulphapyridine solubility is the entropy in water-rich mixtures, most likely as a result of water-structure loss around the drug non-polar moieties by effect of propylene glycol. While for a higher mass fraction of propylene glycol the driving mechanism is the enthalpy, possibly because of the drug solvation increasing due to the co-solvent molecules. The Jouyban–Acree model was effectively applied to represent the density, solubility and thermodynamic properties of sulphapyridine saturated solutions of this system.

Delgado *et al.* [155] did the solubility and solution thermodynamics study of in some ethanol + water mixtures water and the co-solvency of the mixtures was measured at different temperatures from 293.15 to 313.15 K. Thermodynamic quantities of mixing were investigated using some calorimetric values associated with the sulpha drugs fusion process. The higher solubility of these drugs in the ethanol-rich mixtures compared with those rich in water was said to may have been a result of strong self-interaction of water molecules that hinders the introduction of the bulky solutes into the solutions. A non-linear entropy-enthalpy was found for sulphamerazine and sulphamethazine in this system. It was concluded that the data obtained

on this study intensify the physicochemical information concerning anti-parasitic drugs in binary aqueous-co-solvent mixtures.

Perlovicha *et al.* [156] did an analysis on the thermodynamic aspects of solubility process of some sulphonamides, the molar solubilities of the drugs were measured spectrophotometrically and the standard Gibbs energies of the dissolution processes were calculated. The thermodynamic aspects of solubility process of sulpha drugs in water, phosphate buffer with pH 7.4 and n-octanol were analysed with the aid of the isothermal saturated method.

Parihar *et al.* [157] conducted a study on the stability constants and thermodynamic parameters of cadmium complexes with sulphonamides like sulphadiazine, sulphisoxazole, sulphamethazine and sulphathiazole. The thermodynamic parameters; enthalpy change, free energy change and entropy change were calculated in the study. The metal formations were found to be spontaneous, exothermic and not favoured by entropy at higher temperature.

Thakur did a QSAR study on the dissociation constant benzenesulphonamide on a physicochemical approach using surface tension and the physicochemical properties as refractive index, density and surface tension were also measured and significant advancement in the statistics was observed [158]. The results are discussed critically on the basis of regression data and cross-validation parameters. It was concluded that surface tension can be used effectively for modeling pKa of the sulphonamides that were analysed in this study.

Congliang *et al.* [159] determined the temperature dependence of n-octanol-water partition coefficients for some sulphamethazine, sulphadimethoxine, sulphamethoxydiazine, sulphamonomethoxine, sulphamethoxazole, sulphaquinoxaline and sulphachloropyrazine at

different temperatures ranging from 298.15 to 333.15 K. A shake-flask method was used in the determination of the n-octanol-water coefficients and sulphonamides molecules partitioning in this system was said to be mainly an enthalpy driven process. The acquired results showed that the n-octanol-water partition coefficient of each sulphonamide was indirectly proportional temperature.

Hanaee *et al.* [160] did a solubility prediction study of sulphamethoxazole, sulphisoxazole and sulphasalazine in water, 1-propanol, methanol, chloroform, acetone and ethanol at different temperatures using a single determination. The overall percentage of deviations between the predicted and experimental values was found to be equivalent to the ones of the classical two and three parameter models.

Martínez *et al.* [161] conducted a thermodynamic study of the solubility of some sulphonamides in cyclohexane and evaluation of Gibbs energy, entropy and enthalpy was done. The activity coefficients and excess Gibbs energy of the solutes were determined and the results were discussed in terms of solute-solvent interactions. A conclusion was met that the solubilities of sulphonamides in cyclohexane are low than those acquired in other solvents like alcohols or water. Therefore, the activity coefficients in cyclohexane were greater and showed a non-ideal manner in the solvent.

Cárdenas *et al.* [162] applied the Extended Hildebrand solubility approach (EHSA) on the solubility evaluation of sulphanilamide, sulphapyridine and sulphamethizole in propylene glycol and water mixtures at 298.15 K. The predictive character of EHSA was said to be the similar to the one obtained through direct correlation between solubilities of the drug and the same descriptor of polarity of the co-solvent systems.

Martínez *et al.* [163] did an estimation study of the solubility of sulphonamides in octanol and water from entropies of fusion and partition coefficients. Calculated solubilities of the solutions were then compared to those obtained experimentally. The evaluated equations did not give a reasonable estimation of the physicochemical property (solubility) and it was then concluded that the Yalkowsky-Valvani and Jain–Yalkowsky equations need improvement before they can produce reasonable predictions of the aqueous solubility of the studied sulpha drugs.

Delgado *et al.* [164] evaluated the apparent molar volumes of sodium sulphamerazine, sodium sulphamethazine and sodium sulphadiazine in water at several molalities and different temperatures. Densities of aqueous solutions were measured and partial molar expansibilities were also calculated. Due to the negative sign of S_V, it was proposed that the sulpha drugs act mainly as water-structure promoters because of the hydrophobic effect around its non-polar moieties. The positive values obtained of $E_{0\varphi}$ served as evidence that the sulphonamides in this study are hydrophobic solutes and their behaviour can be compared with other drugs and tetraalkylammonium salts. Eventually, it was concluded that the data presented in this study expand the physicochemical information of electrolyte drugs in aqueous solutions.

Hampson *et al.* [165] used the Recirculating equilibrium method to evaluate the solubility of sulphadimethoxine, sulphamerazine and sulphamethazine in supercritical carbon. Sulphamerazine was found to be slightly more soluble than the other sulphonamides. As it was expected the solubility of the sulpha drugs in SC-CO_2 was found to be increasing when pressure was also increasing too. The influence of temperature on the solubility of the sulphonamides displayed that as temperature increased so did the solubility of the drugs at the higher temperature but pressure remained the same.

Perlovich *et al.* [166] did solubility, sublimation, distribution, solvation study using sulphonamides as subject to investigate the molecular interactions in crystals and solutions of those sulphonamides. The transfer processes of the molecules from water to n-octanol were evaluated by using the diagram method and for the n-octanol and sulphonamides solutions the thermochemical parameters of evaporation processes and fusion were acquired. The results obtained in the study were suggested to may play a crucial role on the advance evaluation of distribution of drug molecules and give an improved understanding of biopharmaceutical characteristics of drugs.

Shaabani *et al.* [167] did a novel approach on the synthesis of alkyl and aryl sulphonamides using the reaction of isocyanides, sulphonic acids and water in dichloromethane it was reported that during ambient temperature there were exceptional yields within 20 minutes.
A new and general method was developed for the preparation of these types of sulphonamides beginning with the readily available alkyl and aryl sulphonic acids and isocyanides under impartial conditions without involving a catalyst. The reaction displayed good functional group tolerance and its product isolation and high yielding is up-front.

Muñoz *et al.* [168] conducted an analysis regarding the solubility together with the preferential solvation of sulphamerazine, sulphadiazine and sulphamethazine in a solution of propylene glycol and water at 298.15 K. The parameters of preferential solvation were derived from their properties of thermodynamic solution using IKBI method. It was found that the sulphonamides involved in the study were sensitive to precise solvation effects. However, the precise solute–solvent interactions remained uncertain regardless of the analysis that developed because of the complex molecular structure of the drugs studied. Eventually, it was concluded that the data

reported in the report was to expand the information concerning physicochemical aspects of sulphonamides in binary aqueous-co-solvent mixtures.

De Luca *et al.* [169] did a synthesis study of sulphonamides directly from sulphonic acids with the assistance of microwave. A simple and convenient preparation of sulphonamides directly from its sodium salts or sulphonic acids was reported. The reaction was performed under microwave irradiation and it showed a satisfying functional group tolerance that was accompanied by a high yield. It was then concluded that the method that was used represented a convenient, new and handy preparation of sulphonamides even in big scale, as it utilise approachable reaction conditions and inexpensive and commercially obtainable reagents.

Huang *et al.* [170] conducted an investigation on the mechanistic QSAR models for interpretation of the degradation rates of sulphonamides under UV-photocatalysis. The study focused on ten sulphonamides, employing two photocatalytic systems consisting of nanophase titanium dioxide (TiO_2) with ultraviolet (UV) and TiO_2/activated carbon fiber (ACF) with UV. In light of the partial least squares regression method and the degradation mechanism, for both the two systems ideal QSAR models were established. Mechanistic models showed that the rule of sulphonamides degradation in TiO_2 intensely related to their highest occupied molecular orbital (HOMO), the supreme values of nucleophilic attack and the least values of the utmost negative partial charge on a core-chain atom. While, the apparent adsorption rate constant values and the peak values of -OH radical attack are main factors affecting the rule of sulphonamides degradation in the TiO_2/ACF system. The results obtained designated that the largest apparent sulphonamide degradation rate constant is roughly 5 times as big as that one of the smallest one.

The work done Thakur *et al.* [171] did a QSAR description study on inhibition of *E. Coli* through sulphonamides with the aid of distance-based topological indices. The sulphonamide that was analysed consisted of 39 derivatives with substitution at 2-, 3- and 4- positions as well as having some di-substitution. The results obtained showed that there was no participation of a positive hydrophobic term during the process of inhibition, proposing that the bonding between the sulphonamides and the active centre do not rely on hydrophobic interactions. From the results it was concluded that the distance-based topological indices can be utilised effectively for modeling inhibition of *E.Coli* by sulphonamides and that for the studied set of sulphonamides Szeged index was found to be prominent. As well, that Szeged index produces statistically substantial models when combined with other molecular descriptors.

The objective of the study done by Deodhar *et al.* [172] was to launch a relationship between the β-CAs inhibitory activity for structurally allied sulphonamide derivatives and the physicochemical descriptors in terms of quantitation. The statistically authenticated 2D QSAR model was attained by multiple linear regression (MLR) analysis method. Five descriptors displaying positive and negative correlation with the β-CAs inhibitory activity were involved in the model. This authenticated 2D QSAR model can be utilised for designing of sulphonamides having improved inhibitory properties. A set of 65 molecules of sulphonamide derivatives were exposed to 2D QSAR exploration by means of the MLR to comprehend correlation between the physicochemical parameters and the β-CAI activity. An effective QSAR model for predicting and designing the β-CAI activity of novel sulphonamide derivatives was effectively created with the aid of the MLR method.

Johnson *et al.* [173] conducted QSAR studies of a series of sulphonamides as inhibitors of *Pneumocystis carinii* dihydropteroate synthetase. It was discovered that sulphanilamide and

sulphone have the ability to inhibit dihydropteroate synthetase (DHPS) insulated from *Pneumocystis carinii*. Keeping in mind the end goal to build up a pharmacophoric model for this hindrance, QSAR for sulphonamides active in contrast to DHPS were studied. Precise 50% inhibitory concentrations were gathered for 44 analogs and different parameters for example; partition coefficients and molar refractivity were calculated. Conventional various regression study of this data did not offer an adequate QSAR. The resulting pharmacophore model ought to be significant for comprehension and predicting the bonding of DHPS by new sulphonamides.

Deeb *et al.* [174] did an investigation on the linear and non-linear QSAR approaches for anticipating the inhibitory activities of sulphonamides toward various carbonic anhydrase isozymes were produced taking into account the MLR method, correlation ranking principal component analysis and principal component artificial neural network to classify a set of structurally based numerical descriptors. MLR was utilised to develop linear QSAR models using 53 compounds and their QC descriptors. It was discovered that the hydration energy plays a critical part in bonding of ligands to the CAI isozyme, though the existence of a 5 membered ring was observed as a central point for bonding to the CAII isozyme. Moreover it was discovered that the softness displayed huge impact on the bonding to CAIV isozyme. The predictivity of the models was assessed by cross-validation, utilising an outer test set and risk correlation test. The acquired results give very upright regression models that have great prediction capacity. For the most part, the models attained for modeling the hCAII isozyme inhibitory activity are better over those acquired for modeling the bCAIV and hCAI isozyme inhibitory activities.

Srivastava *et al.* [175] did a QSAR study of 29 benzene sulphonamides as inhibitor of carbonic anhydrase based on QC descriptor, molecular weight, total energy, heat of formation, energy of HOMO, absolute hardness and electronegativity. The objective of the study was to test the correctness of the above mentioned QC parameters as potential biological activity descriptor in the development of QSAR. The study showed that molecular weight, total energy, heat of formation and energy of HOMO of the benzene sulphonamides can be utilised as biological activity descriptors.

2.1 Methods used in measurements of some previous studies

2.1.1 DENSITY

The density ρ of a sample is defined as the division of mass, (m) by volume, (v):

$$\rho = \frac{m}{v} \tag{2.1}$$

Density values are extremely dependent on temperature. Other experimental methods used to measure density are given below:

Magnetic Float Densitometer

The type of procedure of magnetic float densitometer depends on the determination of the stature of a magnetic float in a liquid mixture. The stature of this magnetic float within the sight of an identified magnetic field is an element of the lightness of the fluid. The lightness of the fluid is associated to the density of the fluid. An instrument with an accuracy of 0.000003 $g.cm^{-3}$ has been accounted for and this explains the accuracy of 0.0008 $cm^3.mol^{-1}$ obtained by Franks *et al.* [176]. The magnetic float densitometer with accordance to the design of Franks *et al.* is illustrated in **Figure 2.1**.

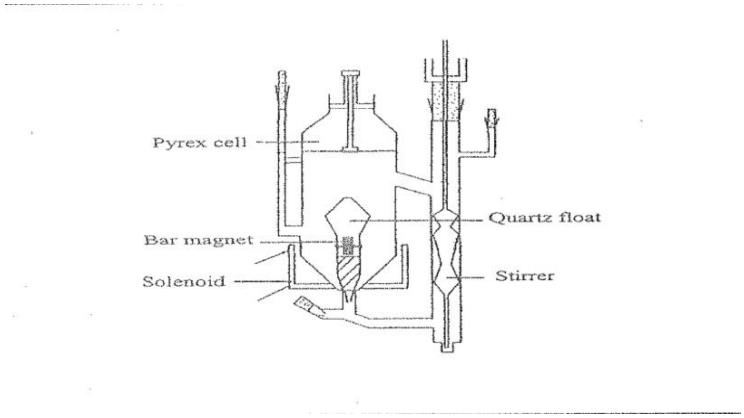


Figure 2.1: Diagram representation of a magnetic float densimeter.

(F. Franks and H.T. Smith, 1967)

Mechanical Oscillating Densitometer

The mechanical oscillating or vibrating tube densitometers attached to digital output displays are broadly utilized in research laboratories and in the chemical industry for density measurements of liquid mixtures and liquids. The frequency of the vibrating tube enclosing a liquid that is exposed to a steady electric stimulation is identified with the density of the liquid.

2.1.2 SPEED OF SOUND

Measuring the sound velocity of liquids is a valuable source of information to spot minor changes in gas configuration or the impact of little changes in [177]. Density and sound velocity are used to calculate apparent molar volumes and apparent molar adiabatic compressibility respectively. Another method used to measure sound velocity are given below.

Mittal Ultrasonic Interferometer M-81G

This is a Mittal multi-frequency ultrasonic interferometer and it is not a basic instrument, the frequency is utilised during determination of the ultrasonic speed in liquids with a level of vulnerability. The frequency for a progression of readings should be taken and the average reading calculated prompting higher errors. It comprises of a:

(a) Great frequency generator, which is intended to energize the quartz plate fixed at the measuring cell's base on its resonance frequency to produce ultrasonic waves in the experimental liquid within the measuring cell. A full scale ammeter detects the adjustments in the present and controls for the sensitivity parameter and the starting changes of the small scale ammeter are given on the great frequency generator.

(b) Measuring cell that is uniquely made double-walled cell for upholding the temperature of the liquid steady amid the experiment. An adequate micrometer screw is given at the top that can elevate or lower the reflector plate in the cell through an identified distance. It has a quartz plate stably placed at the base. A photograph displaying the Ultrasonic Interferometer M-81G and interferometer is given in **Figures 2.2**.

Figure 2.2: Ultrasonic interferometer M-81G.

(Taken from the instruction manual of Mittal Enterprises Ultrasonic Interferometer for Liquids)

2.1.3 VISCOSITY

Viscosity is a function of pressure and temperature. It is an essential characteristic property of entire liquids. During the flow period of a liquid, it possesses an internal resistance to shear or

flow [178]. Viscosity can be referred to as the drag force and it also measure frictional characteristics of liquids [178]. Other experimental methods used to measure viscosity are given below.

Capillary Viscometers

Capillary viscometers measure viscosity by keep track of fluid flow passing through immensely narrow tubes of glass. Inside this viscometer, a fluid is forced or drained through a fine-bore tube, and the determination of viscosity is achieved from the measured flow rate, tube dimensions and applied pressure. **Figure 2.3** is the image of a capillary viscometer.

Figure 2.3: Koehler Constant Temperature Kinematic Viscosity Bath (KV3000).

(Taken from the instruction manual of Koehler KV3000)

Advantages

- Measure accurate viscosities for numerous different liquids.
- Mobile and small.
- Has the ability to use a widespread diversity of capillary tubes within the same viscometer.

Disadvantages

- Not one tube is fit for all viscosities.
- Basic models are to be used for translucent fluids only
- It is challenging to clean its capillary tubes

Falling Ball Viscometers

These types of viscometers determine the viscosity of a Newtonian liquid through measuring the speed of the ball traveling through the liquid. Less liquid viscosity results in low resistance to flow that match to a quicker speed of the moving object. A falling ball viscometer is displayed below in **Figure 2.4**. The liquid is positioned in a container, for instance a graduated cylinder. The movement of a bubble, ball, needle, plate or rod through the liquid is observed. The speed of the object moving is then used to compute the viscosity of the liquid.

Figure 2.4: Brookfield Falling Ball KF30Viscometer.

(Taken from the instruction manual of Brookfield KF30)

Advantages

- Mobile and small.

- Uncomplicated operation

Disadvantages

- Restricted to Newtonian liquids
- Limited to translucent liquids (require the ability to see the motion of the object)

CHAPTER 3

EXPERIMENTAL METHODS

3.1 Chemicals and preparation of samples

The supplier, molecular weight, purity and CAS number of sulphonamides used in this study are presented in **Table 3.1**.

TABLE 3.1: Pure component specifications: suppliers, molecular weight, specified purity and CAS number.

Chemical name	Supplier	Molecular Weight (g/mol)	Mass fraction purity	CAS number
Sulphamethizole	Sigma-Aldrich	270.33	>99.0%	144-82-1
Sulphabenzamide	Sigma-Aldrich	276.30	>99.0%	127-71-9
Sulphaquinoxaline	Sigma-Aldrich	300.37	>99.0%	59-40-5
Sulphachloropyridazine	Sigma-Aldrich	284.72	>99.0%	80-32-0
Methanol	Merck (Pty) Ltd	32.04	>99.9%	67-56-1

An OHAUS mass balance was used to determine the mass of all chemicals with precision of ± 0.0001 g. The uncertainties in molality was ± 0.0004 $mol.kg^{-1}$. Freshly triply distilled and degassed water with a specific conductance greater than 10^{-6} $S.cm^{-1}$ was used for making aqueous solution of sulphonamides. The aqueous solutions of sulphonamides and methanol mixtures were prepared by molality ranging from 0.001and 0.01 $mol.kg^{-1}$ at room temperature. The binary mixtures were transferred via a syringe while being weighed into the stoppard $10cm^3$ glass vials; mixtures were kept in the airtight vials to reduce the adsorption of atmospheric moisture and for the prevention of possible evaporation. The mixtures were shaken in order to make sure that there was complete homogeneity of the compounds. To avoid development of bubbles inside the vibrating tube of the densitometer, sound velocity and viscometer the injections were done slowly. **Figure 3.1** given below is an illustration of the experimental work that was conducted in this study.

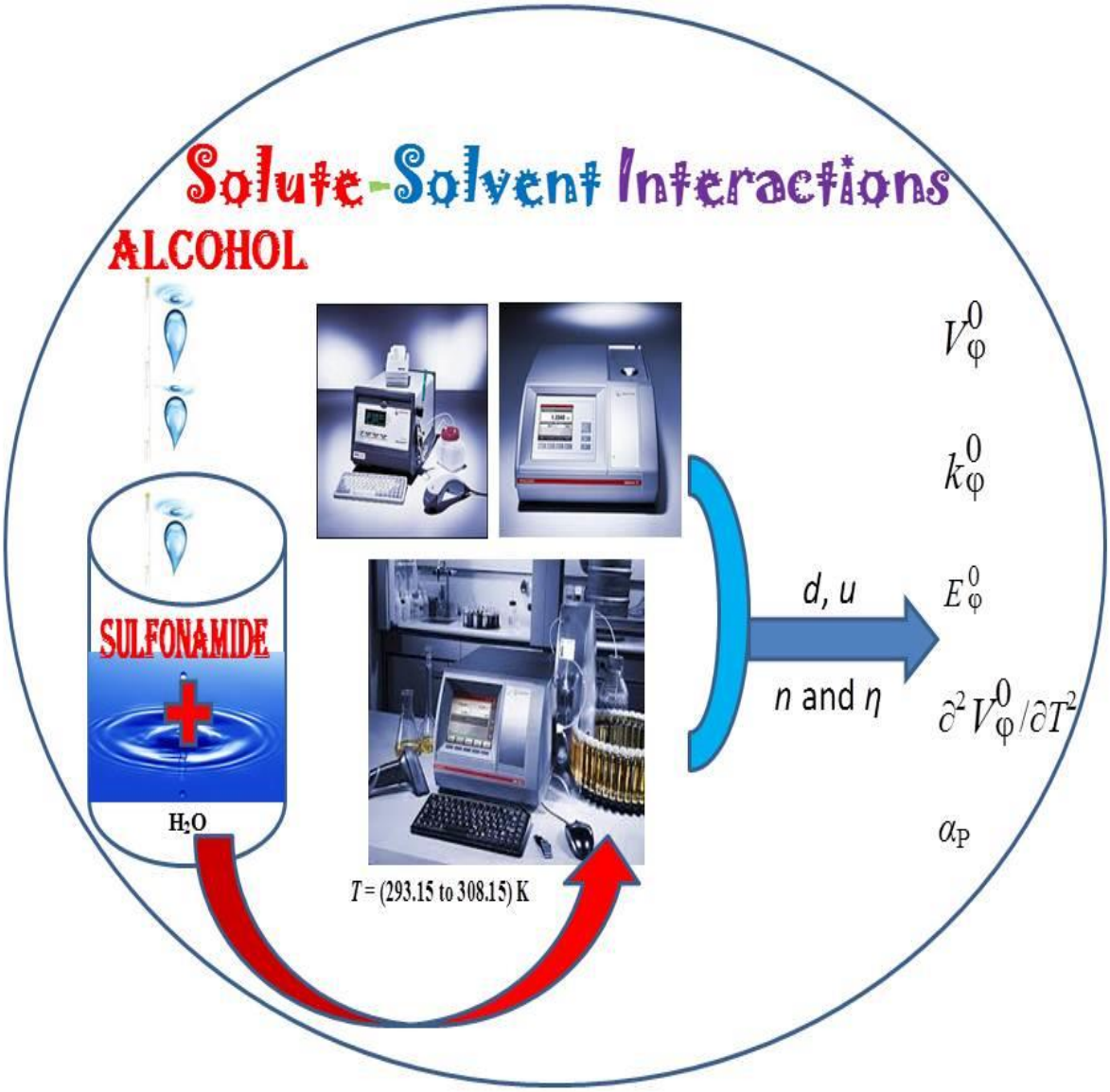


Figure 3.1: The illustration of the experimental work.

3.2 Density and sound velocity measurements

Anton Paar density and sound velocity meter (DSA 5000 M) fitted with the X-sample 452

The sample was put into a U-shaped borosilicate glass tube that vibrates electronically at its characteristic frequency. The characteristic frequency changes depends upon the density of the sample. With the aid of an exact determination of a mathematical conversion and the characteristic frequency, the density of the sample was measurable. The density value was shown on the LCD screen. The DSA 5000 M was attached to a computer loaded with software

that keeps all the measured densities. The sample was introduced into the sound speed measuring cell that is circumscribed by an ultrasonic transmitter on one side and a receiver on another side. The transmitter directs sound waves of an identified period through the sample. The speed of sound was obtained by utilizing the time of the sound waves and the distance between the transmitter and receiver. **Figure 3.2** shows the photograph of the DSA 5000 M fitted with the X-sample 452. The cells for measuring are thermostated precisely, utilizing the Peltier elements and because of the high temperature reliance of sound velocity and density.

Figure 3.2: Density and Sound Velocity Meter (DSA 5000 M) fitted with the X-sample 452.

(Taken from Instruction Manual of Anton Paar DSA 5000 M)

In this work, density and sound velocity of the sulphonamides and methanol mixtures were measured simultaneously using a digital vibrating-tube densimeter and sound velocity analyzer (Anton Paar DSA 5000M) with an accuracy of ± 0.02 K at T = (293.15 to 333.15) K with 10

K intervals and at atmosphere pressure. The two in-one instrument consist of a density cell and a sound velocity cell accordingly consolidating the Anton Paar oscillating U-tube method with an exceedingly precise instrument for the sound velocity measurement. The temperature of the two cells were controlled by a fitted Peltier thermostat. This instrument concurrently determines two independent physical properties utilizing one sample. The samples were taken from the vials with a syringe and immediately injected into the DSA 5000M. Preceding each experimental run, the cell was initially cleaned using ethanol (liquid 1) and then dried with acetone (liquid 2) by means of a completely automatic X-sample 452 Module. X-sample 452 executes a cleaning procedure after measuring each sample. Rinsing liquid 1 dissolves the residues of the sample in the measuring cell of the DSA 5000 M. Rinsing liquid 2 is very volatile and dissolves in liquid 1. Acetone eliminates liquid 1 and is effortlessly evaporated by a stream of dry air in order to speed up drying of the cell. Acetone is a good solvent for eliminating ethanol. Following the rinsing and cleaning, the instrument was calibrated using Ultra-pure water and ambient air. The calibration for the DSA 5000 M was done with the Anton Paar ultrapure water and dry air at 298.15 K. The objective of calibration is to authenticate the accurateness of density and sound velocity measurement. The details of the experimental procedure can be found elsewhere [179-182]. Density, ρ and sound velocity, u, were also measured for a water and methanol system at (293.15 to 333.15) K and at pressure p = 0.1 MPa. The uncertainties in density and sound velocity was 0.06 $kg.m^{-3}$ and 0.4 $m.s^{-1}$.

3.3 Viscosity measurements

Anton Paar Stabinger Viscometer SVM3000

Viscometer SVM3000 is a rotational viscometer with a cylinder geometry that functions in proportion to a distinctive measuring principle. Measurements of rotational viscosity are centred on the measurement of speed and torque. The measuring of viscosity by this instrument

is based on an improved Couette principle with a fast rotating outer tube and an inner measuring bob that rotates more gently. Only 2.5 mL of the sample is required to determine kinematic viscosity, dynamic viscosity and density. A tube enclosed by a very small measuring cell rotates with constant speed. This is the tube that the sample fills during experimental runs. A measuring rotor having a built-in magnet floats within the sample. Low density of the rotor permits it to be centred by the centrifugal force. The rotor swimming freely needs no bearing and in the absence of bearing, friction is absent. **Figure 3.3** displays the photograph of the Anton Paar Stabinger Viscometer SVM3000.

The viscosity of the solutions of all binary mixture and pure solvents was measured by using the Anton Paar SVM3000 fitted with jacketed small sample adapter (SSA) and a thermosel spindle (SC4-18) with accuracy of ±0.02 K in temperature. This instrument has a maximum temperature range of +105^{o} C and a minimum of 20^{o} C lower than ambient. Reproducibility of the instrument viscosity is 0.35%. Prior to each experimental run the cell was first rinsed and cleaned with distilled water and then dried with acetone. After rinsing and cleaning the instrument, it was calibrated using Millipore quality water and air. The details of the experimental procedure can be found elsewhere [183]. The uncertainties in viscosity measurements was 0.0004 mPa.s^{-1}. The uncertainties were calculated for all parameters using two different methods such as error propagation as well as NIST methods.

Figure 3.3: Anton Paar Stabinger Viscometer SVM3000.

(Taken from Instruction Manual of Anton Paar SVM3000)

CHAPTER 4

RESULTS AND DISCUSSION

4.1. Density, sound velocity and viscosity

The density, ρ, sound velocity, u, and viscosity, η, for the mixtures of methanol in aqueous solutions of sulphamethizole, sulphabenzamide, sulphaquinoxaline and sulphachloropyridazine at (293.15, 303.15, 313.15, 323.15 and 333.15) K and at pressure p = 0.1 MPa were measured and presented in **Table 4.1**.

TABLE 4.1

Density, ρ, sound velocity, u, and viscosity, η, of methanol in aqueous solution of sulphamethizole, sulphabenzamide, sulphaquinoxaline and sulphachloropyridazine at (293.15, 303.15, 313.15, 323.15 and 333.15) K and at pressure p = 0.1 MPa.

m (mol·kg^{-1})	ρ (kg.m^{-3})	u (m·s^{-1})	η (mPa.s)
Methanol + aqueous solution of 0.01 M sulphamethizole			
		T = 293.15K	
0.0589	997.86	1483.8	1.6345
0.2512	996.30	1487.4	1.6525
0.7459	993.96	1493.4	1.6702
0.9937	992.57	1497.1	1.6877
1.3620	990.74	1502.0	1.7332
2.5164	985.24	1517.7	1.7848
3.7683	980.09	1532.6	1.8677
5.0445	975.43	1544.2	1.9628

0.0589	995.30	1509.5	1.4759
0.2512	994.13	1511.8	1.5115
0.7459	991.38	1516.8	1.5291
0.9937	989.96	1519.4	1.5483
1.3620	988.09	1523.1	1.5677
2.5164	982.42	1534.2	1.6393
3.7683	977.00	1544.6	1.6837
5.0445	972.04	1552.9	1.7920

T = 313.15K

0.0589	991.87	1528.9	1.3713
0.2512	990.61	1530.7	1.3833
0.7459	987.90	1534.0	1.3699
0.9937	986.46	1535.9	1.3867
1.3620	984.55	1538.3	1.4029
2.5164	978.72	1545.6	1.4445
3.7683	973.06	1552.0	1.4789
5.0445	967.85	1556.6	1.5577

T = 323.15 K

0.0589	987.68	1544.4	1.2767
0.2512	986.40	1545.6	1.2755
0.7459	983.66	1547.6	1.2553
0.9937	982.20	1548.8	1.2592

1.3620	980.25	1550.2	1.2649
2.5164	974.25	1553.2	1.2934
3.7683	968.39	1555.0	1.3149
5.0445	962.94	1559.9	1.3694

T = 333.15K

0.0589	982.83	1552.7	1.1012
0.2512	981.41	1553.5	1.1004
0.7459	978.76	1555.2	1.1104
0.9937	977.27	1556.7	1.1189
1.3620	975.28	1557.2	1.1020
2.5164	969.11	1558.1	1.1038
3.7683	963.05	1560.0	1.1342
5.0445	957.32	1563.5	1.1804

Methanol + aqueous solution of 0.01 M sulphabenzamide

T = 293.15 K

0.0604	997.91	1483.6	1.5134
0.2528	996.79	1486.3	1.5119
0.7542	994.01	1493.2	1.5766
0.9960	992.70	1496.6	1.5683
1.3544	990.01	1504.0	1.5967
2.5235	984.35	1520.2	1.7168
3.7622	980.35	1531.8	1.7816

5.0519	974.53	1547.5	1.9627

T = 303.15 K

0.0604	995.36	1505.5	1.4036
0.2528	994.23	1508.5	1.4030
0.7542	991.43	1516.6	1.4016
0.9960	990.10	1518.1	1.3954
1.3544	987.35	1524.5	1.4185
2.5235	981.48	1536.1	1.5396
3.7622	977.28	1544.0	1.5294
5.0519	971.07	1554.3	1.6810

T = 313.15 K

0.0604	991.92	1528.9	1.2209
0.2528	990.79	1530.3	1.2264
0.7542	987.95	1533.9	1.2172
0.9960	986.60	1535.7	1.2053
1.3544	983.79	1539.3	1.2473
2.5235	977.74	1546.8	1.3485
3.7622	973.36	1551.7	1.3607
5.0519	966.82	1557.2	1.4055

T = 323.15 K

0.0604	987.74	1542.5	1.1529
0.2528	986.59	1543.4	1.1009

0.7542	983.71	1545.6	1.0883
0.9960	982.34	1546.6	1.0747
1.3544	979.47	1548.7	1.0966
2.5235	973.25	1552.7	1.1723
3.7622	968.69	1554.9	1.2107
5.0519	961.87	1560.2	1.2432

T = 333.15 K

0.0604	982.90	1551.9	1.0310
0.2528	981.73	1552.3	1.0062
0.7542	978.72	1554.2	1.0007
0.9960	977.39	1555.7	0.9538
1.3544	974.45	1556.4	0.9643
2.5235	968.08	1559.0	0.9738
3.7622	963.28	1559.9	1.0023
5.0519	956.27	1563.1	1.0380

Methanol + aqueous solution of 0.001 M sulphaquinoxaline

T = 293.15 K

0.0604	998.01	1484.2	1.0607
0.2523	996.50	1487.6	1.0731
0.7549	993.77	1494.6	1.1379
0.9980	992.86	1500.8	1.1501
1.3592	991.05	1505.8	1.1814

2.4912	985.78	1519.4	1.2841
3.7737	980.49	1532.0	1.3699
4.9785	976.06	1544.2	1.4716

T = 303.15 K

0.0604	995.46	1510.0	0.9687
0.2523	993.94	1512.6	0.9743
0.7549	991.18	1517.7	1.0310
0.9980	990.25	1520.9	1.0300
1.3592	988.41	1523.0	1.0476
2.4912	982.96	1533.7	1.1192
3.7737	977.41	1544.2	1.1699
4.9785	972.70	1552.3	1.2384

T = 313.15 K

0.0604	992.02	1529.6	0.7958
0.2523	990.49	1531.4	0.7962
0.7549	987.69	1534.9	0.8255
0.9980	986.75	1536.0	0.8275
1.3592	984.87	1538.5	0.8369
2.4912	979.27	1545.5	0.8871
3.7737	973.49	1551.9	0.9560
4.9785	968.53	1556.4	0.9979

T = 323.15 K

0.0604	987.83	1546.4	0.6399
0.2523	986.29	1547.5	0.6551
0.7549	983.45	1549.4	0.6749
0.9980	982.49	1550.1	0.6880
1.3592	980.57	1551.5	0.7012
2.4912	974.82	1552.2	0.7268
3.7737	968.83	1555.1	0.7510
4.9785	963.65	1560.4	0.7896

T = 333.15 K

0.0604	982.98	1555.1	0.5119
0.2523	981.42	1556.4	0.5292
0.7549	978.95	1558.8	0.5495
0.9980	977.56	1559.2	0.5620
1.3592	975.60	1560.6	0.5810
2.4912	969.69	1561.4	0.5949
3.7737	963.50	1562.1	0.6167
4.9785	958.12	1564.5	0.6358

Methanol + aqueous solution of 0.001 M sulphachloropyridazine

T = 293.15 K

0.0621	997.35	1486.9	1.0602
0.2527	996.19	1488.7	1.0773
0.7550	994.02	1493.2	1.1135

1.0019	992.38	1497.7	1.1476
1.3478	990.93	1501.8	1.1777
2.5012	985.63	1517.9	1.2514
3.7856	980.40	1531.7	1.3628
5.0391	975.86	1544.2	1.4666

T = 303.15 K

0.0621	994.80	1512.1	0.9710
0.2527	993.63	1513.4	0.9729
0.7550	991.44	1516.6	1.0029
1.0019	989.77	1519.9	1.0272
1.3478	988.30	1522.9	1.0311
2.5012	982.81	1534.4	1.0827
3.7856	977.33	1544.0	1.1600
5.0391	972.49	1552.2	1.2092

T = 313.15 K

0.0621	991.35	1531.0	0.7873
0.2527	990.17	1531.8	0.7862
0.7550	987.96	1534.0	0.8072
1.0019	986.26	1536.2	0.8220
1.3478	984.76	1538.2	0.8299
2.5012	979.11	1545.8	0.8943
3.7856	973.41	1553.7	0.9337
5.0391	968.32	1556.2	0.9996

T = 323.15 K

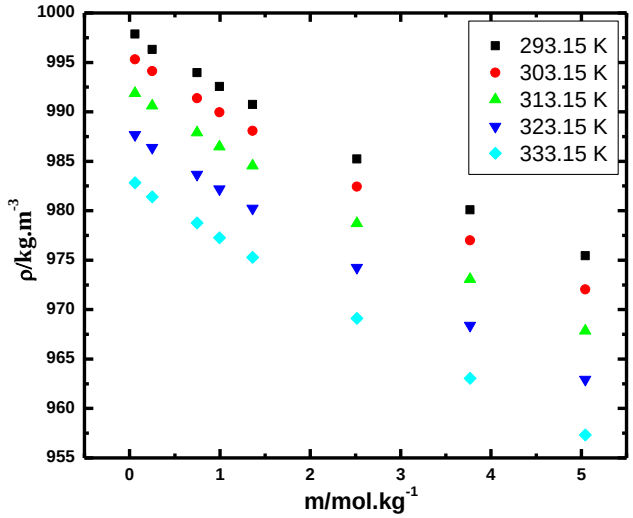
0.0621	987.16	1544.2	0.6525
0.2527	985.97	1544.9	0.6512
0.7550	983.72	1545.7	0.6694
1.0019	982.00	1547.0	0.6728
1.3478	980.46	1548.2	0.6868
2.5012	974.65	1552.3	0.7348
3.7856	968.75	1555.0	0.7509
5.0391	963.43	1560.2	0.7992

T = 333.15 K

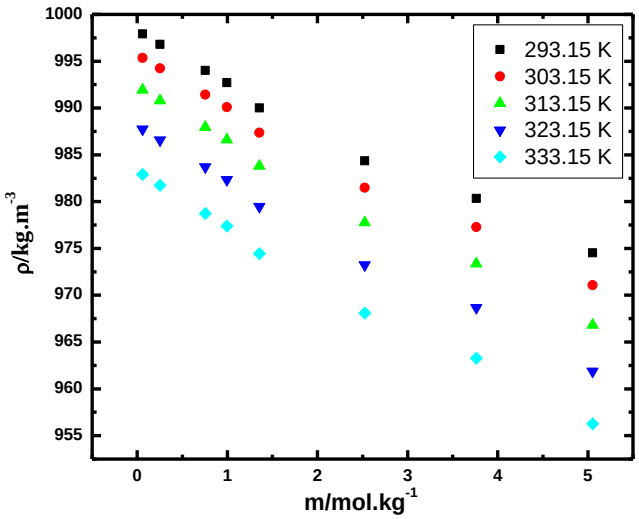
0.0621	982.30	1552.8	0.5371
0.2527	981.10	1553.0	0.5440
0.7550	978.81	1552.5	0.5610
1.0019	977.05	1553.0	0.5734
1.3478	975.49	1555.3	0.5806
2.5012	969.52	1558.3	0.5868
3.7856	963.42	1560.0	0.5989
5.0391	957.90	1564.2	0.6336

The values of ρ, u and η for methanol in 0.01, 0.01, 0.001 and 0.001 mol.kg^{-1} aqueous solutions of sulphamethizole, sulphabenzamide, sulphaquinoxaline and sulphachloropyridazine, respectively, against the molalities of methanol at different temperatures are plotted in **Figures 4.1-4.3 (a, b, c, d)**.

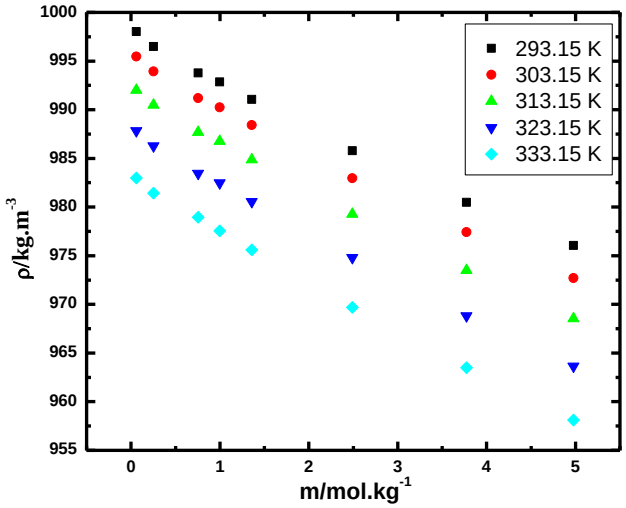
From Figures 4.1 (a, b, c, d), it is observed that the values of ρ decreases with an increases the temperature and concentration of methanol. The decrease in the value of ρ indicates the existence of weak molecular interaction between solute and solvent molecules. The data in **Table 4.1**, show that the ρ values of the aqueous solutions of sulphonamide derivatives in methanol at studied temperatures follow the order : sulphaquinoxaline > sulphabenzamide > sulphamethizole > sulphachloropyridazine. From this order, the increase in ρ values for sulphonamide derivatives in methanol mixtures is possibly due to the increase in the dipole-dipole interactions between the sulphonamide derivatives and methanol-water [184]. The thermo-physical properties of sulphonamide derivatives depends on the nature and structure of the sulphonamide drug. Among the drugs used, sulphaquinoxaline shows higher ρ values as compared to sulphabenzamide, sulphamethizole or sulphachloropyridazine, respectively, which implies that there is strong interactions of quinoxaline group in sulphaquinoxaline with methanol or water.



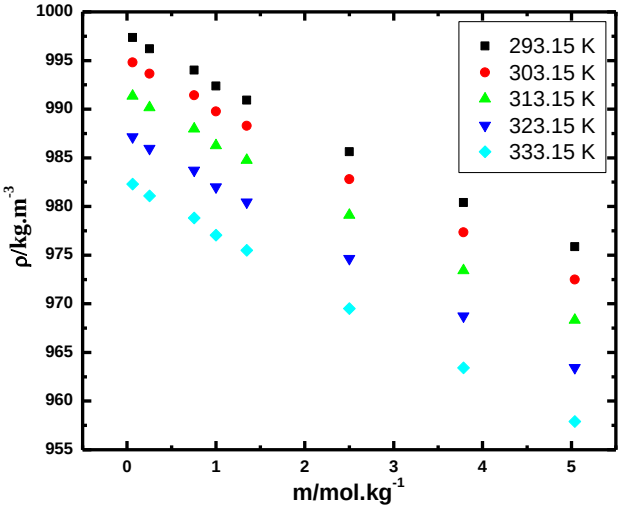
(a) Sulphamethizole



(b) Sulphabenzamide



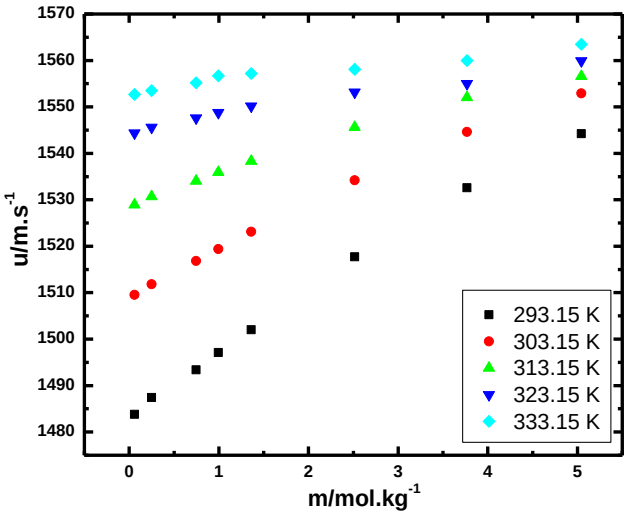
(c) Sulphaquinoxaline



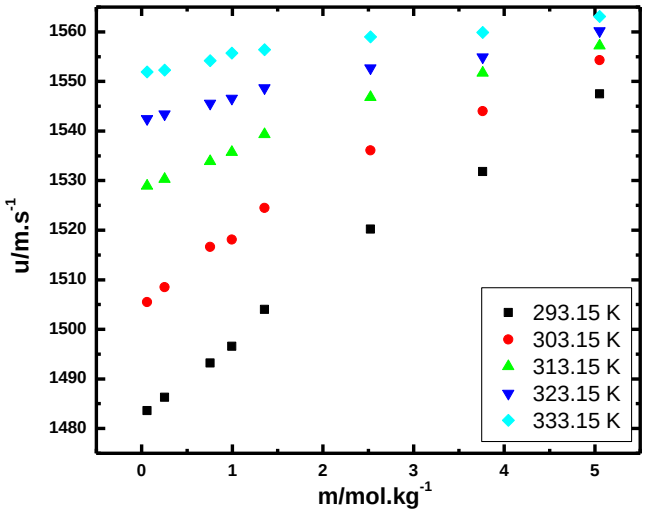
(d) Sulphachloropydizine

Figure 4.1: Density (ρ) for the mixtures of methanol in aqueous solution of sulphonamide derivatives at (293.15, 303.15, 313.15, 323.15 and 333.15) K.

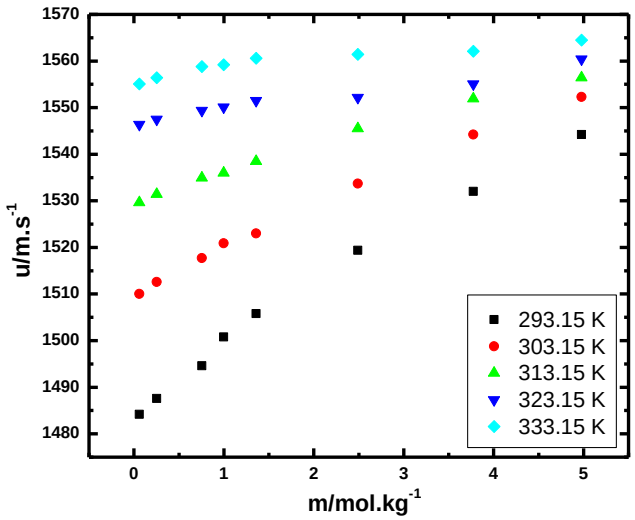
Figures 4.2 (a, b, c, d) show that the values of *u* increase with the increase in both concentration and temperature. The sound velocity increases or decreases depending on the structure and properties of solute [184]. Therefore, the solutes that increase the *u* are said to be structure makers while those that decrease *u* are structure breakers. Methanol increases the sound velocity, therefore it acts as a structure maker. The increase in *u* indicates that the interaction between solute and solvent is becoming more dominant [184]. Due to the substitution of weak intermolecular attraction between solvent molecules by stronger intermolecular interactions. This shows that the solvent-solvent interaction is traded by solute-solvent interaction. As it can be shown in **Figure 4.2** and **Table 4.1** at all investigated temperatures, the *u* values of aqueous solution of sulphonamide derivative in methanol follow the order: sulphachloropyridazine > sulphaquinoxaline > sulphamethizole ≥ sulphabenzamide. With regard to *u*, the small variation in values of *u* for sulphonamide derivatives with methanol affected with both size and shape of drugs, water and methanol content and have significant influence on the molecular interactions in the mixture.



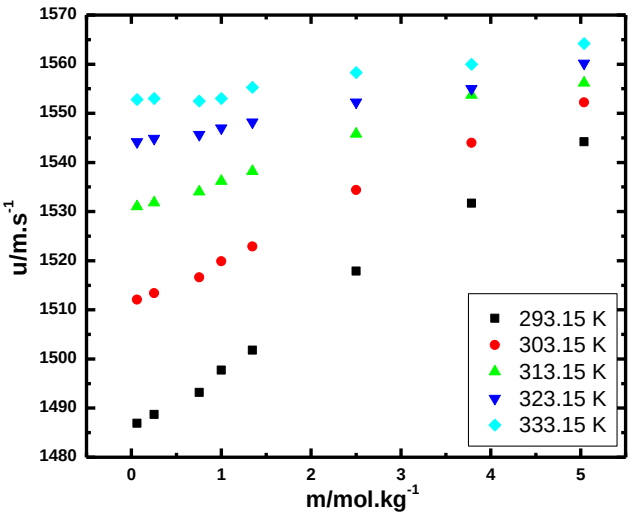
(a) Sulphamethizole



(b) Sulphabenzamide



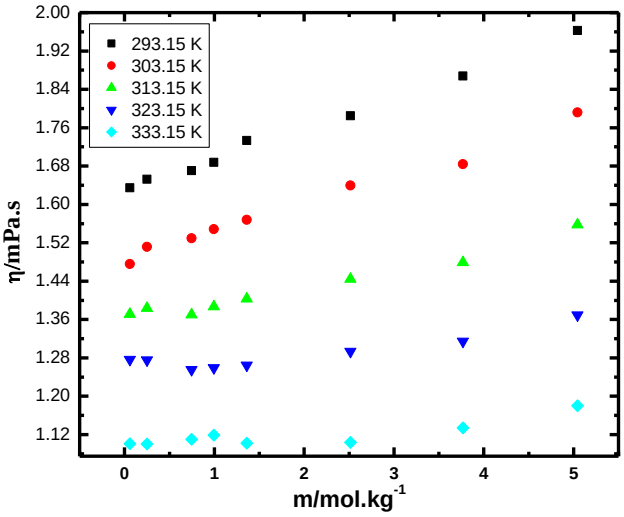
(c) Sulphaquinoxaline



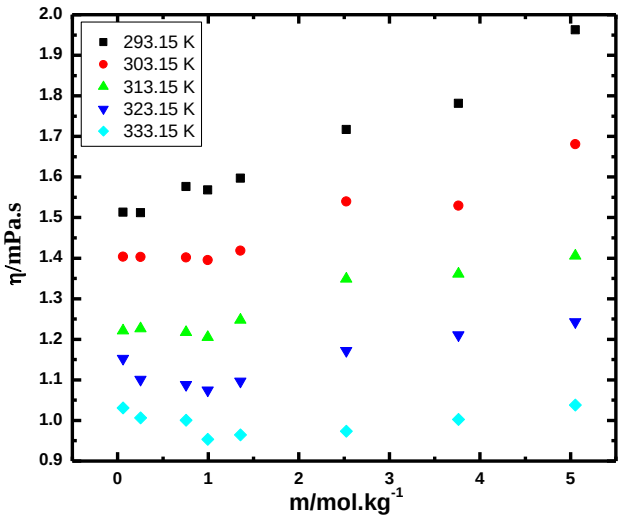
(d) Sulphachloropydizine

Figure 4.2: Sound velocity (u) for the mixtures of methanol in aqueous solution of sulphonamide derivatives at (293.15, 303.15, 313.15, 323.15 and 333.15) K.

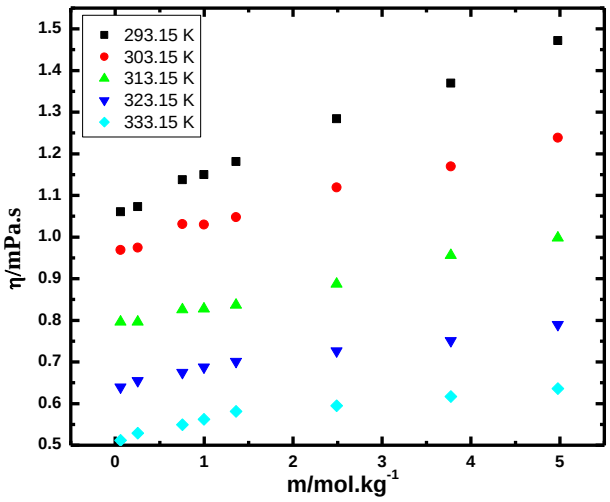
Figures 4.3 (a, b, c, d) shows that the values of η increase with decreasing temperature and with concentration, there is no proper trend that has been found. The increase in temperature might have led to the increase in the kinetic energy of molecules within the solution, which then decrease the solute–solvent interaction. Hence, the forces of attraction between the solvent and solute molecules should overcome contraction with an expansion in the arbitrary movement of molecules and ions as temperature increases which causes fast movement of molecules and ions into the void sites [185]. A decrease like this in interactions seems to be liable for the reduction in viscosity with an increase in temperature. The data in **Table 4.1** and **Figure 4.3** show that the values of η for aqueous of the solution sulphonamide derivatives with methanol follows the order: sulphamethizole > sulphaquinoxaline > sulphachloropyridazine > sulphabenzamide. Interestingly, sulphamethizole drug shows higher η values with methanol than compared to the rest of sulphonamide derivatives at studied temperatures. From these result, it can be interpreted that there is the formation of strong columbic interaction between the ions of sulphamethizole in water when mixed with the methanol.



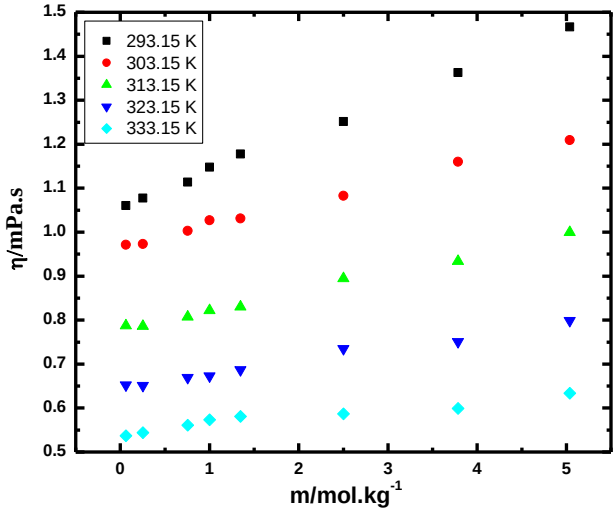
(a) Sulphamethizole



(b) Sulphabenzamide



(c) Sulphaquinoxaline



(d) Sulphachloropydizine

Figure 4.3: Viscosity (η) for the mixtures of methanol in aqueous solution of sulphonamide derivatives at (293.15, 303.15, 313.15, 323.15 and 333.15) K.

4.2. Apparent molar quantities

The apparent molar volume, V_φ, and apparent molar adiabatic compressibility, k_φ, were calculated from the experimental densities and sound velocities using the following equations:

$$V_\varphi = \frac{M}{\rho} - \frac{(\rho - \rho_0)}{m\rho\rho_0} \quad , \tag{4.1}$$

$$k_\varphi = \frac{(k_S \rho_0 - k_{S0}\rho)}{m\rho\rho_0} + \frac{k_S M}{\rho} \quad , \tag{4.2}$$

$$k_S = \frac{1}{\rho u^2} \quad , \tag{4.3}$$

where m is the molality (mol.kg^{-1}) of methanol in aqueous solutions of sulphamethizole or sulphabenzamide or sulphaquinoxaline or sulphachloropyridazine, M is the molar mass of the solvent (aqueous sulphonamide) (kg.mol^{-1}) and ρ, ρ_0, $k_{S\,0}$, and k_S are the densities (kg.m^{-3}), coefficient of adiabatic compressibility (Pa^{-1}) of reference solute (desired molality methanol and (methanol + sulphonamide derivative + water) ternary mixtures, respectively and u is the sound velocity of the mixture. The subsequent values of V_φ, and k_φ for the mixture of methanol in aqueous solution of sulphamethizole, sulphabenzamide, sulphaquinoxaline and sulphachloropyridazine at (293.15, 303.15, 313.15, 323.15 and 333.15) K and at pressure p = 0.1 MPa are also presented in **Table 4.2**.

TABLE 4.2

Apparent molar volume, V_φ and apparent molar adiabatic compressibility k_φ of methanol in aqueous solution of sulphamethizole, sulphabenzamide, sulphaquinoxaline and sulphachloropyridazine at (293.15, 303.15, 313.15, 323.15 and 333.15) K and at pressure p = 0.1 MPa.

m (mol.kg^{-1})	$10^3 \times V_\varphi$ (m^3·mol^{-1})	$10^{-5} \times k_\varphi$ (m^3·mol^{-1}·Pa^{-1})
Methanol + aqueous solution of 0.01M sulphamethizole		
	T = 293.15K	
0.0589		17.5
	-4.40	
0.2512		17.6
	-1.00	
0.7459		17.8
	-0.31	
0.9937		17.9
	-0.23	
1.3620		18.0
	-0.15	
2.5164		18.5
	-0.07	
3.7683		19.0
	-0.03	
5.0445		19.4
	-0.01	
	T = 303.15 K	
0.0589		17.9
	-4.65	
0.2512		18.0
	-1.09	
0.7459		18.1
	-0.36	

0.9937		18.2
	-0.27	
1.3620		18.4
	-0.20	
2.5164		18.7
	-0.10	
3.7683		19.1
	-0.07	
5.0445		19.4
	-0.05	

T = 313.15 K

0.0589		18.2
	-4.86	
0.2512		18.3
	-1.13	
0.7459		18.4
	-0.38	
0.9937		18.5
	-0.28	
1.3620		18.6
	-0.20	
2.5164		18.9
	-0.11	
3.7683		19.1
	-0.07	
5.0445		19.3
	-0.05	

T = 323.15 K

0.0589		18.4
	-5.06	

0.2512		18.5
	-1.18	
0.7459		18.6
	-0.39	
0.9937		18.6
	-0.29	
1.3620		18.7
	-0.21	
2.5164		18.9
	-0.11	
3.7683		19.1
	-0.07	
5.0445		19.3
	-0.05	

T = 333.15 K

0.0589		18.5
	-5.24	
0.2512		18.5
	-1.19	
0.7459		18.6
	-0.38	
0.9937		18.7
	-0.27	
1.3620		18.7
	-0.19	
2.5164		18.9
	-0.09	
3.7683		19.0
	-0.04	
5.0445		19.2
	-0.02	

Methanol + aqueous solution of 0.01M sulphabenzamide

T = 293.15 K

0.0604		17.5
	-4.33	
0.2528		17.5
	-1.03	
0.7542		17.8
	-0.34	
0.9960		17.9
	-0.26	
1.3544		18.1
	-0.19	
2.5235		18.6
	-0.10	
3.7622		18.9
	-0.06	
5.0519		19.4
	-0.05	

T = 303.15 K

0.0604		17.8
	-4.53	
0.2528		17.9
	-1.08	
0.7542		18.1
	-0.36	
0.9960		18.2
	-0.27	
1.3544		18.4
	-0.20	
2.5235		18.8
	-0.10	
3.7622		19.1
	-0.07	
5.0519		19.5
	-0.05	

T = 313.15 K

0.0604		18.2
	-4.74	
0.2528		18.3
	-1.13	
0.7542		18.4
	-0.37	
0.9960		18.5
	-0.28	
1.3544		18.6
	-0.21	
2.5235		18.9
	-0.11	
3.7622		19.1
	-0.07	
5.0519		19.4
	-0.05	

T = 323.15 K

0.0604		18.4
	-4.94	
0.2528		18.4
	-1.18	
0.7542		18.5
	-0.39	
0.9960		18.6
	-0.29	
1.3544		18.7
	-0.21	
2.5235		18.9
	-0.11	
3.7622		19.0
	-0.07	
5.0519		19.3
	-0.05	

T = 333.15 K

0.0604		18.5
	-5.14	

0.2528		18.5
	-1.22	
0.7542		18.6
	-0.41	
0.9960		18.6
	-0.31	
1.3544		18.7
	-0.22	
2.5235		18.9
	-0.12	
3.7622		19.0
	-0.08	
5.0519		19.2
	-0.06	

Methanol + aqueous solution of 0.001M sulphaquinoxaline

T = 293.15 K

0.0604		17.5
	-4.32	
0.2523		17.6
	-1.03	
0.7549		17.8
	-0.34	
0.9980		18.0
	-0.26	
1.3592		18.1
	-0.19	
2.4912		18.5
	-0.10	
3.7737		18.9
	-0.06	
4.9785		19.3
	-0.05	

T = 303.15 K

0.0604		17.9
	-4.53	
0.2523		18.0
	-1.08	
0.7549		18.2
	-0.36	
0.9980		18.3
	-0.27	
1.3592		18.4
	-0.20	
2.4912		18.7
	-0.10	
3.7737		19.1
	-0.07	
4.9785		19.4
	-0.05	

T = 313.15 K

0.0604		18.2
	-4.74	
0.2523		18.3
	-1.13	
0.7549		18.4
	-0.37	
0.9980		18.5
	-0.28	
1.3592		18.6
	-0.21	
2.4912		18.8
	-0.11	
3.7737		19.1
	-0.07	
4.9785		19.3
	-0.05	

T = 323.15 K

0.0604		18.5
	-4.94	
0.2523		18.5
	-1.18	
0.7549		18.6
	-0.39	
0.9980		18.7
	-0.29	
1.3592		18.7
	-0.21	
2.4912		18.9
	-0.11	
3.7737		19.0
	-0.07	
4.9785		19.3
	-0.05	
	T = 333.15 K	
0.0604		18.4
	-5.22	
0.2523		18.5
	-1.24	
0.7549		18.6
	-0.41	
0.9980		18.6
	-0.31	
1.3592		18.7
	-0.23	
2.4912		18.8
	-0.12	
3.7737		19.0
	-0.08	
4.9785		19.1
	-0.06	

Methanol + aqueous solution of 0.001M sulphachloropyridazine

T = 293.15 K

0.0621		17.5
	-4.20	
0.2527		17.6
	-1.03	
0.7550		17.8
	-0.34	
1.0019		17.9
	-0.26	
1.3478		18.0
	-0.19	
2.5012		18.5
	-0.10	
3.7856		18.9
	-0.06	
5.0391		19.3
	-0.05	

T = 303.15 K

0.0621		17.8
	-4.66	
0.2527		17.8
	-1.14	
0.7550		17.9
	-0.38	
1.0019		18.0
	-0.28	
1.3478		18.1
	-0.21	
2.5012		18.5
	-0.11	
3.7856		18.8
	-0.07	
5.0391		19.1
	-0.05	

T = 313.15 K

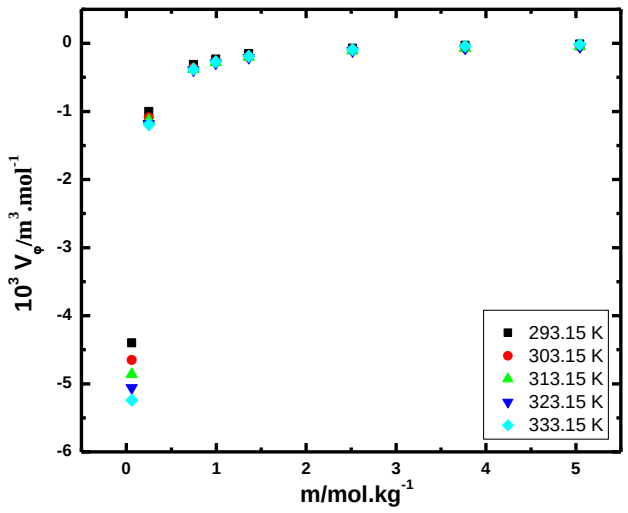
0.0621		18.3
	-4.60	
0.2527		18.3
	-1.13	
0.7550		18.4
	-0.37	
1.0019		18.5
	-0.28	
1.3478		18.6
	-0.21	
2.5012		18.9
	-0.11	
3.7856		19.1
	-0.07	
5.0391		19.3
	-0.05	

T = 323.15 K

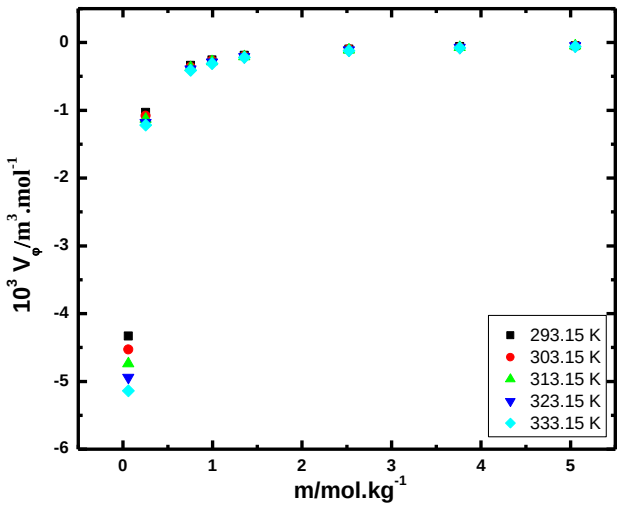
0.0621		18.4
	-4.80	
0.2527		18.5
	-1.17	
0.7550		18.5
	-0.39	
1.0019		18.6
	-0.29	
1.3478		18.7
	-0.22	
2.5012		18.9
	-0.11	
3.7856		19.0
	-0.07	

5.0391		19.3
	-0.05	
	T = 333.15 K	
0.0621		18.5
	-4.99	
0.2527		18.5
	-1.22	
0.7550		18.5
	-0.41	
1.0019		18.6
	-0.30	
1.3478		18.7
	-0.22	
2.5012		18.9
	-0.12	
3.7856		19.0
	-0.08	
5.0391		19.2
	-0.06	

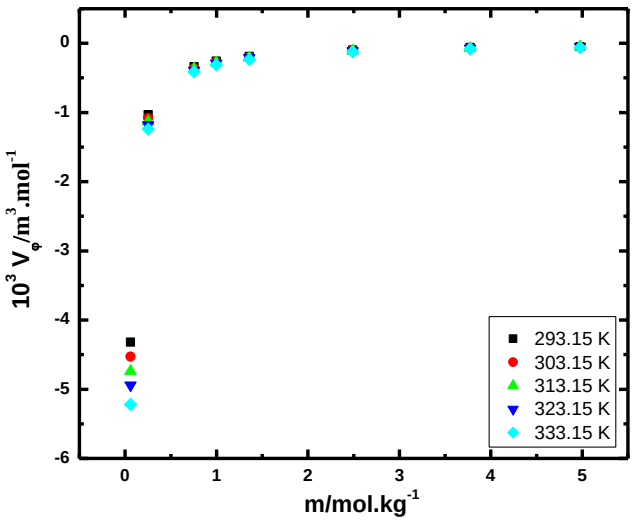
The values given in **Table 4.2** of V_φ and k_φ, for methanol in 0.01, 0.01, 0.001 and 0.001 mol.kg-1, aqueous solutions of sulphamethizole, sulphabenzamide, sulphaquinoxaline and sulphachloropyridazine, respectively, against the molalities of methanol at different temperatures have been plotted in **Figures 4.4 (a, b, c, d)** and **4.5 (a, b, c, d),** respectively. The apparent molar volume, V_φ, and apparent molar adiabatic compressibility, k_φ, are very helpful parameters in the investigation of solute-solute and solute-solvent interactions.



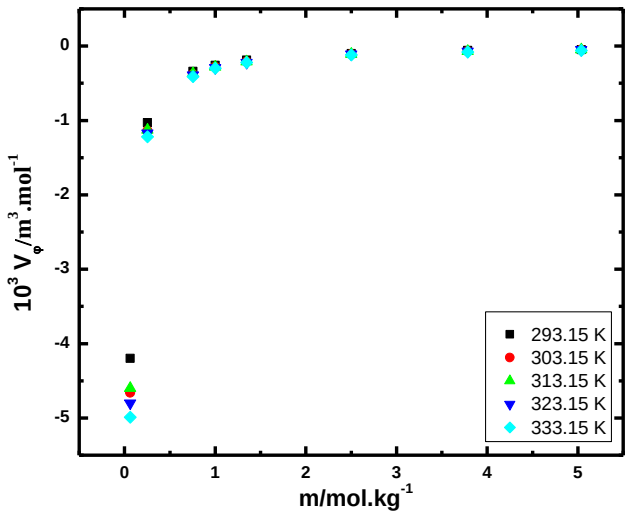
(a) Sulphamethizole



(b) Sulphabenzamide



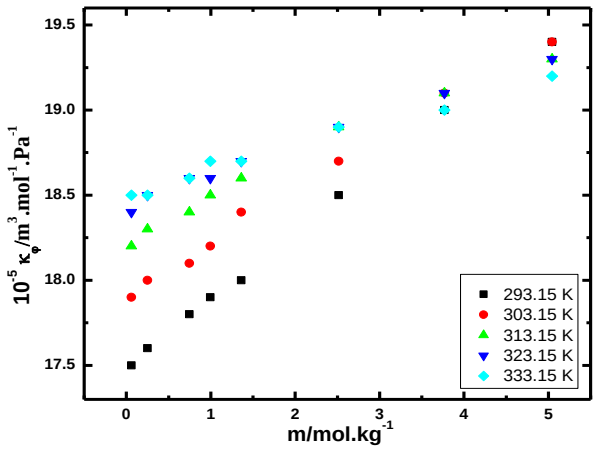
(c) Sulphaquinoxaline



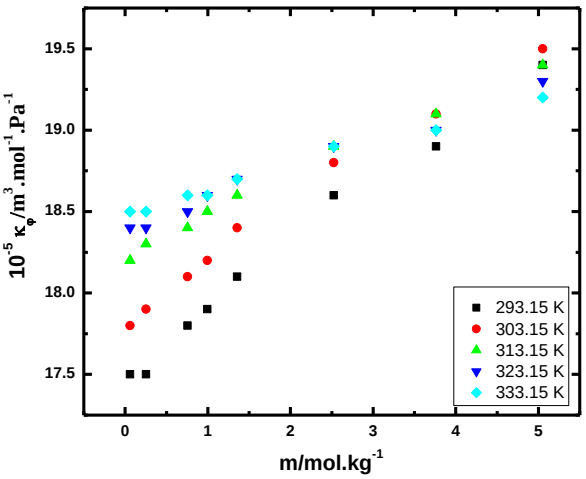
(d) Sulphachloropydizine

Figure 4.4: Apparent molar volume (V_φ) of methanol in aqueous solution of sulphamethizole, sulphabenzamide, sulphaquinoxaline and sulphachloropyridazine at (293.15, 303.15, 313.15, 323.15 and 333.15) K and at pressure p = 0.1 MPa.

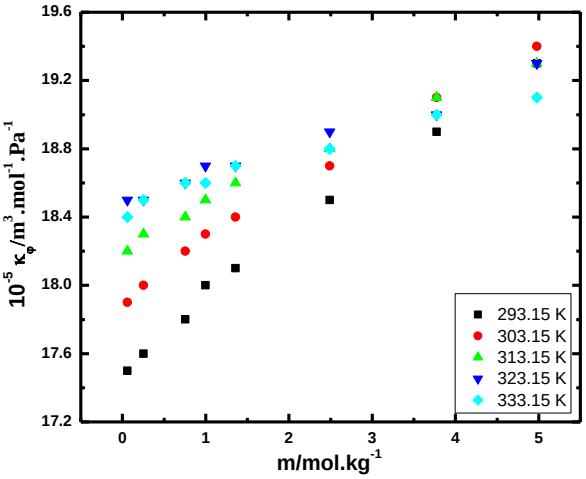
The values of V_φ are explained as the limiting volume that a substance occupy in one mole of the other substance; in this limit, solute molecules are enclosed only by the solvent molecules [186]. **Figure 4.4 (a, b, c, d)**, indicate that apparent molar volume decreases with an increase in temperature for all the systems. The V_φ values are negative and increase with increasing concentration for all systems. For all the systems with low molality of solute, the solute molecules are encircled by solvent molecules showing strong (solute-solvent) interactions and increasing the solute concentration, the (solute-solute) interaction increases causing large V_φ values [187]. The V_φ values are negative and increase with increasing concentration which suggests that order of overall structure is reduce in solution [187]. The apparent molar volumes are negative and increase with concentration which indicates that the total structural order is reduced in solution. The V_φ values are larger at high concentration which shows that the overall structural order is enriched in solution at higher concentration of methanol [188]. Plots of apparent molar volume against molality of aqueous sulphonamides in methanol at various studied temperatures demonstrate that the apparent molar volume of aqueous sulphonamides is non-linear with molality and that this factor is relies greatly on the molality of methanol together with temperature. A similar non-linear (curvy) relationship between apparent molar volume and concentration was been observed in these studies [189, 190].



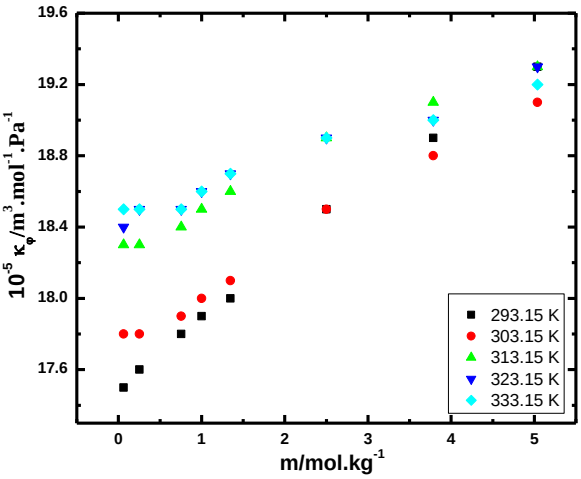
(a) Sulphamethizole



(b) Sulphabenzamide



(c) Sulphaquinoxaline



(d) Sulphachloropydizine

Figure 4.5: Apparent molar adiabatic compressibility (k_{φ}) of methanol in aqueous solution of sulphamethizole, sulphabenzamide, sulphaquinoxaline and sulphachloropyridazine at 293.15, 303.15, 313.15, 323.15 and 333.15) K and at pressure p = 0.1 MPa.

Figure 4.5 (a, b, c, d), show that the apparent molar adiabatic compressibility values increase with an increase in temperature and concentration for all systems at different temperatures. The k_{φ} values are positive for all the systems which point out that methanol rich region is more compressible as related with bulk solution [185]. The positive k_{φ} values are associated with the weak attractive interactions between the solute and solvent.

Addition of the solute drops the compressibilty of the solvent molecules around the solute, which usually increases internal pressure [191]. Positive adiabatic compressibilities of aqueous sulphonamides are explained with regards to the rising compressibility of the methanol as a result of electrostrictive forces in the vicinity of the sulphonamides molecules [192]. Sound velocity decrease when the packing of the molecules is less dense and compressibility of these solutions increase [193].

It is imperative to take into consideration that even though V_{φ} to some degree indicates the interactions occurring in the solution, they can be greatly affected, by the size of the molecule [194]. The intrinsic size of a molecule in a solution may be affected by various aspects, for instance a reform in the bond angles that may be a result of an alteration in the physicochemical properties of the solvent at different molalities [194]. Then again, k_{φ} can preferably display the influence of the interactions occurring between the solvent and solute together with the hydration of the molecules [194].

4.3. Apparent molar quantities at infinite dilution

Supposing that the aqueous solutions of each sulphonamide work are similar to those of 1:1 aqueous electrolyte in the dilute region, the concentration reliance of V_φ and k_φ can be explained utilizing the Redlich–Mayer equation in the dilute region as equations (4.4) and (4.5) [195, 196] and the variety in apparent molar volume V_φ and apparent adiabatic compressibility k_φ with concentration can be sufficiently represented by the equations given below:

$$V_\varphi = V_\varphi^0 + S_v m^{1/2} + B_v m \tag{4.4}$$

$$k_\varphi = k_\varphi^0 + S_k m^{1/2} + B_k m \tag{4.5}$$

where V_φ^0 and k_φ^0 are the limiting values of apparent molar volume and apparent adiabatic compressibility, respectively and are often considered equal to the infinite dilution partial molar volume and infinite dilution partial molar adiabatic compressibility. The terms S_v, B_v, S_k and B_k represent the values of the experimental slopes that provide substantial information concerning the intermolecular interactions that occur in solutions. The values of V_φ^0 and fitting parameters S_v and B_v values were obtained by using the least-squares analysis of equation (4.4) and their values for each mixture at the studied experimental temperatures together with standard deviations are listed in **Table 4.3**.

TABLE 4.3

Limiting apparent molar volumes V_φ^0, and fitting parameters S_v and B_v, of methanol in aqueous sulphamethizole, sulphabenzamide, sulphaquinoxaline and sulphachloropyridazine at (293.15, 303.15, 313.15, 323.15 and 333.15) K and at pressure p = 0.1 MPa.

T (K)	10^3 x V_φ^0 ($m^3 \cdot mol^{-1}$)	10^3 x S_v ($m^3 \cdot mol^{-3/2} \cdot kg^{1/2}$)	10^3 x B_v ($m^3 \cdot mol^{-2} \cdot kg$)	10^3 x σ
Methanol + aqueous solution of 0.01M sulphamethizole				
293.15	-2.57	4.14	-1.31	1.20
303.15	-2.70	4.35	-1.38	1.25
313.15	-2.82	4.54	-1.44	1.31
323.15	-2.94	4.73	-1.50	1.37
333.15	-3.06	4.92	-1.56	1.42
Methanol + aqueous solution of 0.01M sulphabenzamide				
293.15	-2.55	4.05	-1.28	1.16
303.15	-2.67	4.24	-1.34	1.21
313.15	-2.79	4.43	-1.40	1.27
323.15	-2.91	4.63	-1.46	1.33
333.15	-3.03	4.81	-1.52	1.37
Methanol + aqueous solution of 0.001M sulphaquinoxaline				
293.15	-2.57	4.15	-1.33	1.15
303.15	-2.70	4.35	-1.40	1.21
313.15	-2.82	4.55	-1.46	1.26
323.15	-2.91	4.63	-1.46	1.33
333.15	-3.11	5.01	-1.61	1.39
Methanol + aqueous solution of 0.001M sulphachloropyridazine				
293.15	-2.50	3.98	-1.26	1.12
303.15	-2.77	4.42	-1.40	1.24
313.15	-2.74	4.36	-1.38	1.22
323.15	-2.86	4.55	-1.44	1.28
333.15	-2.97	4.73	-1.50	1.33

Table 4.3, shows that the values of V_φ^0 are negative for all aqueous solutions of sulphonamide with methanol systems at the experimental temperatures. As V_φ^0 is a measure of solute-solvent interactions, the negative values of V_φ^0 indicate a weak solute-solvent interactions [197]. The solute-solvent interactions decrease with an increase in temperature for all systems. The V_φ^0 values increase in the following order: sulphamethizole ≈ sulphabenzamide > sulphachloropyridizine ≈ sulphaquinoxaline which may possibly be due to the effect of replacement of different groups attached to sulpha derivatives. These results indicate that from

sulphamethizole to sulphabenzamide to sulphachloropyridizine to sulphaquinoxaline there is an increase in the strengths of solute-solvent interactions that lead to an increase in the electrostriction effect, consequently in the reduction of volume and hence the augmentation of elasticity of the solution [198-202]. The lower V_{φ}^{0} value for sulphaquinoxaline can be described in terms of the more noticeable 'electrostriction' effect that occurs within the system [203] and also the 'electrostriction' effect, the size of the sulpha derivatives together with the degree of steric hindrance of molecules are extra factors which impact on the V_{φ}^{0} values [204]. The S_v values are positive for all systems at all temperature as shown in Table 4, due to the hydrophobicity of the sulphonamides and it gives the idea that there is a distant balance between hydration of the polar and hydrophobic parts of the molecules prompting the detected large net hydrophobicity [205]. The S_v value increases with increasing temperature for all the systems. The solute-solute interactions shows the order sulphaquinoxaline > sulphamethizole > sulphabenzamide > sulphachloropyridazine. The (solute-solute) interaction increases with increasing temperature for all the systems. The S_v values are positive and large for aqueous solution of sulphonamides in methanol at studied temperatures. Since S_v measures the solute-solute interactions, the results show the existence of very strong solute-solute interactions [206]. These interactions increase with increasing temperature which may be credited to the decrease in solvation of molecules; meaning that more and more of the solute molecules accommodated in the empty spaces are left during the packing of bulky associated molecules of the solvent with increasing temperature.

Table 4.3, shows that B_v values decrease with increasing temperature indicating the increased non-electrostatic interactions of aqueous solutions of sulphonamide and methanol at high temperatures. The B_v values are negative at all temperature for each systems illustrating an

increase in the solute-solvent interactions for all systems and the instantaneous release of any of the sulphonamide derivative to the bulk solvent [207].

The values of k_{φ}^{0} and fitting parameters S_k and B_k values were attained by using the least-squares analysis of equation (4.5) and their values for each mixture at the studied experimental temperatures together with standard deviations are presented in **Table 4.4**.

TABLE 4.4

Limiting apparent molar adiabatic compressibility k_{φ}^{0}, and fitting parameters S_k and B_k, of methanol in aqueous sulphamethizole, sulphabenzamide, sulphaquinoxaline and sulphachloropyridazine at (293.15, 303.15, 313.15, 323.15 and 333.15) K and at pressure p = 0.1 MPa.

T (K)	10^{-5} x k_{φ}^{0} ($m^3 \cdot mol^{-1} \cdot Pa^{-1}$)	10^{-5} x S_k ($m^3 \cdot mol^{-3/2} \cdot kg^{1/2}\ Pa^{-1}$)	10^{-5} x B_k ($m^3 \cdot mol^{-2} \cdot kg \cdot Pa^{-1}$)	10^{-5} x σ
Methanol + aqueous solution of 0.01M Sulphamethizole				
293.15	17.4	0.9	-0.04	0.03
303.15	17.9	0.7	-0.05	0.04
313.15	18.2	0.7	-0.09	0.02
323.15	18.4	0.4	-0.03	0.03
333.15	18.5	0.4	-0.03	0.03
Methanol + aqueous solution of 0.01M Sulphabenzamide				
293.15	17.4	1.0	-0.09	0.06
303.15	17.8	0.9	-0.09	0.04
313.15	18.2	0.6	-0.05	0.03

323.15	18.4	0.4	-0.03	0.05
333.15	18.5	0.3	-0.02	0.03
Methanol + aqueous solution of 0.001M Sulphaquinoxaline				
293.15	17.5	0.9	-0.08	0.04
303.15	17.9	0.7	-0.06	0.03
313.15	18.2	0.6	-0.05	0.03
323.15	18.5	0.3	0.00	0.05
333.15	18.4	0.4	-0.05	0.03
Methanol + aqueous solution of 0.001M Sulphachloropyridazine				
293.15	17.5	0.9	-0.05	0.02
303.15	17.7	0.6	-0.02	0.04
313.15	18.2	0.6	-0.06	0.03
323.15	18.4	0.4	-0.01	0.05
333.15	18.5	0.3	-0.02	0.05

It is known that solutes that bring less electrostriction lead to an increase in the compressibility of the solution [208, 209]; which is revealed by the positive values of k_{φ}^{0} in all systems shown in **Table 4.4**. Hydrophilic solutes frequently display positive compressibilities as a result of the ordering they prompt in the water structure [205, 200]. The compressibility of hydrogen bonded structures differs depending on the kind of the H-bonds present [209]. Additionally, as the probability of flexible H-bond formation seem to be accountable for instigating an extra compressible environment in the aqueous medium, the positive values of compressibilities for sulpha drugs show an overall compression in the solution volumes that is due to changing degrees of hydrophobic hydration or electrostriction [205]. The positive k_{φ}^{0} values of all

systems may be interpreted in terms of increase in the compressibility of the solution compared to the pure solvent sulphamethizole or sulphabenzamide or sulphaquinoxaline or sulphachloropyridazine. Positive limiting apparent adiabatic compressibility of sulphamethizole, sulphabenzamide, sulphaquinoxaline and sulphachloropyridazine systems are due to the solvent intrinsic compressibility being larger than the penetration effect. This shows that the sulphamethizole or sulphabenzamide or sulphaquinoxaline or sulphachloropyridazine molecules being released from methanol present less resistance to compression than the bulk solvent. The S_k and B_k values have the similar meaning like S_v and B_v.

4.4. Partial molar quantities of transfer

The partial molar volumes of transfer ΔV_{φ}^{0} and partial molar adiabatic compressibility of transfer Δk_{φ}^{0} from water to aqueous solutions of sulphonamide derivatives were calculated using equation given below:

$$\Delta Y_{\Phi}^{0} = Y_{\Phi}^{0}(in\ aqueous\ co-solute\ solution) - Y_{\Phi}^{0}(in\ water) \qquad (4.6)$$

where Y_{Φ}^{0} represents V_{φ}^{0} and k_{φ}^{0}, their resultant values have been reported in **Table 4.5**.

TABLE 4.5

Partial molar volume of transfer ΔV_{φ}^{0} , and partial molar adiabatic compressibility of transfer Δk_{φ}^{0} of methanol in aqueous sulphamethizole, sulphabenzamide, sulphaquinoxaline and sulphachloropyridazine at (293.15, 303.15, 313.15, 323.15 and 333.15) K and at pressure p = 0.1 MPa.

T (K)	10^3 x ΔV_{φ}^{0} ($m^3 \cdot mol^{-1}$)	10^{-5} x Δk_{φ}^{0} ($m^3 \cdot mol^{-1} \cdot Pa^{-}$
	Methanol + aqueous solution of 0.01M Sulphamethizole	
293.15	-0,131	-0.2
303.15	-0,141	-0.1
313.15	-0,144	-0.1
323.15	-0,149	0.1
333.15	-0,154	0.1
	Methanol + aqueous solution of 0.01M Sulphabenzamide	
293.15	-0,111	-0.2
303.15	-0,111	-0.2
313.15	-0,114	-0.1
323.15	-0,119	0.1
333.15	-0,124	0.1
	Methanol + aqueous solution of 0.001M Sulphaquinoxaline	
293.15	-0,044	-0.1
303.15	-0,045	-0.1
313.15	-0,047	-0.1
323.15	-0,049	0.1
333.15	-0,101	-0.1
	Methanol + aqueous solution of 0.001M Sulphachloropyridazine	
293.15	-0,061	-0.1
303.15	-0,211	-0.3
313.15	-0,064	-0.1
323.15	-0,069	0.1

333,15	-0,064	0,1

The density and sound velocity measured (presented in **Appendix 1**) of the (methanol + water) system were used to calculate the partial molar volumes of transfer ΔV_{φ}^{0} and partial molar adiabatic compressibility of transfer Δk_{φ}^{0} from aqueous solutions of sulphonamide derivatives at different temperatures are given in appendix 1 as **Table 1 A** and **2 A** as well as **Figure 1 A**. **Table 4.5** shows that the $\Delta_{Y_{\Phi}}^{0}$ values are free from (solute-solute) interactions, thus providing information about (solute-solvent) interactions [211]. The values of ΔV_{φ}^{0} are negative and increase with increasing temperature for all systems. The negative values of ΔV_{φ}^{0} of methanol in aqueous solution of sulphamethizole or sulphabenzamide or sulphaquinoxaline or sulphachloropyridazine may be associated with decreasing solute-solvent interactions at infinite dilution [212]. Witnessing that the ΔV_{φ}^{0} values are negative and in general decrease with increasing temperature, this provides an understanding that there is an existence of weak solute-solvent interactions that are experienced at higher temperatures [213].

The values of Δk_{φ}^{0} increase with temperature for sulphamethizole, sulphabenzamide, sulphaquinoxaline and sulphachloropyridazine and this may be attributed to increase of electrostricted water molecules around the sulphamethizole or sulphabenzamide sulphaquinoxaline or sulphachloropyridazine [214]. The negative Δk_{φ}^{0} values show that the water molecules surrounding the sulphonamides have less compressibility than the one existing in bulk and decrease as temperature increase, which may be the result of the melting of inflexible hydration structures around the sulphonamide derivatives [213]. The studied sulphonamides derivatives contain these hydrophilic groups O, N and S, which have weak

partial charges and the interactions of this kind are accountable for loosening monomeric water molecules to bulk, where they are rearranged to cluster and provide a negative influence to Δk_{φ}^{0} values [213].

4.5. Limiting apparent molar expansivities

The temperature dependence of V_{φ}^{0} can be expressed as [205]:

$$V_{\varphi}^{0} = A + BT + C T^{2} \tag{4.7}$$

where *A, B* and *C* are empirical parameters and *T* is the temperature. The limiting apparent molar expansibility E_{φ}^{0} can be attained by differentiating Eq. (4.7) with respect to temperature

$$E_{\varphi}^{0} = \left(\frac{\partial V_{\varphi}^{0}}{\partial T} \right)_{\mathrm{P}} = B + 2CT \tag{4.8}$$

The E_{φ}^{0} values are given in **Table 4.6**, which are negative for all aqueous solutions of sulphonamide with methanol mixtures.

TABLE 4.6

The limiting apparent molar expansibility, E_{φ}^{0} of methanol in aqueous sulphamethizole, sulphabenzamide, sulphaquinoxaline and sulphachloropyridazine at (293.15, 303.15, 313.15, 323.15 and 333.15) K and at pressure p = 0.1 MPa.

Solute	Solvent	10^3 x E_{φ}^{0} ($m^3 \cdot mol^{-1} \cdot K^{-1}$)				
		T = 293.15 K	T = 303.15 K	T = 313.15 K	T=323.15 K	T =333.15 K
Methanol	Sulphamethizole	-0,0128	-0,0125	-0,0122	-0,0119	-0,0116

Methanol	Sulphabenzamide	-0,0124	-0,0123	-0,0121	-0,0120	-0,0120
Methanol	Sulphaquinoxaline	-0,0098	-0,0113	-0,0129	-0,0144	-0,0160
Methanol	Sulphachloropyrizidine	-0,0152	-0,0128	-0,0103	-0,0079	-0,0054

The E_{φ}^{0} values give a significant indicator of solute–solvent interactions [215]. An increase in the E_{φ}^{0} values with increase in temperature show that there is an increases in thermal agitation, leading to sulphamethizole, sulphabenzamide or sulphachloropyridizine molecules that are released from methanol, thus increasing the solution volume to a larger magnitude than for the pure solvent [215]. In the sulphaquinoxaline system, the E_{φ}^{0} values decrease with increase in temperature. The E_{φ}^{0} values decrease with increasing temperature in the sulphaquinoxaline with water system, because at higher temperature there are less solvent molecules bound on the solute resulting in expansibility of the solute in solutions being weaker [216].

It was observed that at each temperature, E_{φ}^{0} values for aqueous solutions of sulphonamides are negative and increase with temperature for the other three systems except the one of sulphaquinoxaline. Negative expansibility (i.e. decreasing volume with increasing temperature) is a characteristic property of aqueous solutions of hydrophobic hydration and this would decrease the solution volume slightly less rapidly than that of pure water, hence E_{φ}^{0} would be negative [217].

Structural changes in solution are sensitive to temperature, hence E_{φ}^{0} becomes a very vital parameter in understanding solute-solvent interactions. Positive E_{φ}^{0} illustrate the dominance of solvophobic interaction over electrostriction [218]. The negative values of E_{φ}^{0} indicate the

dominance of electrostriction over solvophobic interaction and that there are weak (solute-solvent) interactions present in all solutions investigated [218].

The structure-making ability of methanol in aqueous sulphonamide solutions is credited to the coordination of water molecules around molecules of methanol through hydrophilic hydration, hydrophobic hydration and electrostriction [213]. When the molality increases, the interactions between solvent and solute increases and the electrostricted and hydrated water molecules around the hydrophobic and hydrophilic groups relaxes [213].

Previously, it has been indicated by different researchers that S_v is not the exclusive measure for the determination of structure making or structure breaking ability of any solute [212]. Hepler established a method of examining the sign of $\left(\partial^2 V_\varphi^0 \middle/ \partial T^2\right)_p$ for numerous solutes in terms of long-range structure breaking and making capability solutes in aqueous solutions by means of the general thermodynamic expression given in equation (4.9) [205].

According to the Hepler's equation [219], the E_φ^0 is a linear function of temperature:

$$T\left(\frac{\partial^2 V_\varphi^0}{\partial T^2}\right)_p = -\left(\frac{\partial C_p}{\partial P}\right)_T \tag{4.9}$$

It has been shown that the sign of $\left(\partial^2 V_\varphi^0 \middle/ \partial T^2\right)_p$ (Helper's constant) is a better criterion in characterizing the long range structure making and breaking capability of the solute in solution [220]. A positive sign on the Helper's constant represent structure making and the negative sign represent structure breaking effect on the solvent [221]. The values of $\left(\partial^2 V_\varphi^0 \middle/ \partial T^2\right)_p$ are 0.000029, 3×10^{-18}, 0,0002 and 0,0002 for methanol in aqueous solution of sulphamethizole or

sulphabenzamide or sulphaquinoxaline or sulphachloropyridizine, respectively. The $\left(\partial^2 V_\varphi^0 \middle/ \partial T^2\right)_P$ values of are positive for all sulphonamides.

Since these are water based mixtures, interstitials might not be easily accessed due to the resilient internal hydrogen bonds between the protic water molecules [195]. The values of $\left(\partial^2 V_\varphi^0 \middle/ \partial T^2\right)_P$ for aqueous solution of sulphamethizole or sulphabenzamide are very small for these systems. This is credited to the absence of caging or packing effects at a lower concentration [217]. All $\left(\partial^2 V_\varphi^0 \middle/ \partial T^2\right)_P$ values are positive for all systems. Thus, the solute methanol acts as a structure maker in aqueous solution of sulphamethizole or sulphabenzamide or sulphaquinoxaline or sulphachloropyridizine. The evidence of the relationship between the Hepler's constant and microscopic structure is given in the literature [222].

4.6. Thermal expansion coefficients

The isobaric thermal expansion coefficient, α_P, of the solutes was calculated using the apparent molar volume and apparent molar expansibility at infinite dilution data. The results obtained for the limiting apparent molar volumes, V_φ^0, and limiting apparent molar expansibility, E_φ^0, were used in the calculations of the isobaric thermal expansion coefficients, α_P, of the sulphonamides aqueous solutions and methanol systems studied.

$$\alpha_P = \frac{1}{V_\varphi^0}\left(\frac{\partial V_\varphi^0}{\partial T}\right)_P = \frac{E_\varphi^0}{V_\varphi^0} \tag{4.10}$$

The isobaric thermal expansion coefficients, α_P, are also given in **Table 4.7** and it has been noted that the α_P values show a decrease with increasing temperature for sulphamethizole, sulphabenzamide and sulphachloropyridizine, though the opposite for sulphaquinoxaline. Additional, the α_P values of methanol in aqueous solution of the studied sulphonamides have been contrasted and have the order: sulphaquinoxaline > sulphamethizole > sulphabenzamide > sulphachloropyridizine.

TABLE 4.7

The isobaric thermal expansion coefficients α_p of methanol in aqueous sulphamethizole, sulphabenzamide, sulphaquinoxaline and sulphachloropyridazine at (293.15, 303.15, 313.15, 323.15 and 333.15) K and at pressure p = 0.1 MPa.

Solute	Solvent	10^3 x α_P (K^{-1})				
		T = 293.15 K	T = 303.15 K	T = 313.15 K	T=323.15 K	T =333.15 K
Methanol	Sulphamethizole	0,0050	0,0046	0,0043	0,0041	0,0038
Methanol	Sulphabenzamide	0,0047	0,0045	0,0043	0,0041	0,0040
Methanol	Sulphaquinoxaline	0.0042	0.0044	0.0047	0.0049	0.0051
Methanol	Sulphachloropyridizine	0.0060	0.0046	0.0038	0.0028	0.0019

4.7. Viscometric properties

The Jones–Dole empirical equation (Equation (4.11)) describes the relative viscosities of electrolyte solutions as functions of their concentrations [223]. Marcus and Jenkins defined the origin of this equation [195] is shown below:

$$\eta_r = \frac{\eta}{\eta_0} = 1 + Ac^{\frac{1}{2}} + Bc + Dc^2 \qquad (4.11)$$

where η is the viscosity of the solute (methanol) and η_0 is the viscosity of the solvent (sulphonamide derivative + water). C is the concentration (molality) in moles per unit volume. The adaptation of molality (m) to molality (c) was done through using the density values and A, B and D are constants.

If A and D-coefficients are ignored in equation (4.11) becomes equivalent to the Einstein's viscosity equation of non-electrolyte solutions [224]. So the extended Jones-Dole equation take this form:

$$\eta_r = 1 + Bc \tag{4.12}$$

Equation (4.12) was used to calculate the B-coefficients for the mixtures of methanol in aqueous solutions of sulphamethizole, sulphabenzamide, sulphaquinoxaline and sulphachloropyridazine at (293.15, 303.15, 313.15, 323.15 and 333.15) K and at pressure *p* = 0.1 MPa are presented in Table 3. The viscosity B-coefficient is a tool used to provide information concerning the solvation of solute in solution and their effect on the structure of solvent in the vicinity of solute molecules [225]. The size and shape of the hydrated molecule impact predominantly the magnitude and sign of the B-coefficient [226]. The data reported in **Table 4.8** shows that viscosity B-coefficients are positive at all concentrations for all the studied aqueous solutions of sulphonamides in methanol and signify the structure-making ability behaviour of the solute (methanol) in solution. B-coefficients can give direct evidence concerning the structural effects they have in solutions [225]. Although, dB/dT is an improved criterion to determine the effect of solute-solvent interaction as the structure maker if the solute have negative values and structure breaker if the solute have positive value for it on structure of solutions compared to the B-coefficient [227, 228]. The dB/dT values are given in **Table 4.8**. The positive values of dB/dT are an indication of the solute being structure breaker while negative values are an indication of the solute being a structure maker [225]. It is

observed that dB/dT values from **Table 4.8** are positive for sulphabenzamide, yet are negative for sulphamethizole, sulphaquinoxaline and sulphachloropyridazine in aqueous solution of methanol. So, we can classify sulphabenzamide as structure breakers, while sulphamethizole, sulphaquinoxaline and sulphachloropyridazine are structure makers.

TABLE 4.8

B-coefficients and Temperature coefficient, dB/dT, of methanol in aqueous solution of sulphamethizole, sulphabenzamide, sulphaquinoxaline and sulphachloropyridazine at (293.15, 303.15, 313.15, 323.15 and 333.15) K and at pressure p = 0.1 MPa.

T (K)	B-cofficient ($m^3 \cdot mol^{-1}$)	Temperature coefficient, dB/dT ($m^3 \cdot mol^{-1} \cdot K^{-1}$)
	Methanol + aqueous solution of 0.01M Sulphamethizole	
293.15	0,1049	
303.15	0,0872	
313.15	0,0638	-0,00009
323.15	0,0457	
333.15	0,0368	
	Methanol + aqueous solution of 0.01M Sulphabenzamide	
293.15	0,0870	
303.15	0,0550	
313.15	0,0423	0.00010
323.15	0,0296	
333.15	0,0044	
	Methanol + aqueous solution of 0.001M Sulphaquinoxaline	
293.15	0,0827	
303.15	0,0538	
313.15	0,0425	-0,00001

323.15	0,0281	
333.15	0,0232	
	Methanol + aqueous solution of 0.001M Sulphachloropyridizine	
293.15	0,0807	
303.15	0,0488	
313.15	0,0433	-0,00004
323.15	0,0298	
333.15	0,0167	

CHAPTER 5

CONCLUSION

In the present work, a detailed study of density, sound velocity and viscosity of methanol in aqueous solution of sulphamethizole, sulphabenzamide, sulphaquinoxaline and sulphachloropyridizine have been reported in the temperature range (293.15 to 333.15) K and at pressure p = 0.1 MPa. Derived properties like apparent molar volumes, V_φ , apparent molar adiabatic compressibilities, k_φ , and viscosity B-coefficients have been calculated and these parameters have been interpreted for the several sorts of interactions occurring in solution. These positive values of B-coefficient denote the structure-making capability behaviour of the solute. The values of V_φ^0 were negative showing that there is weak solute–solvent interactions. The solute–solvent interactions decreased with an increase in temperature for all systems. The S_v value were positive and increased with increasing temperature for all the mixtures, while indicating that solute-solute interactions follow the order; sulphabenzamide > sulphamethizole > sulphaquinoxaline > sulphachloropyridizine. The S_v and S_k values show that there are very strong solute-solute interactions. The positive k_φ^0 values of all systems may be interpreted in terms of increase in the compressibility of the solution compared to the pure solvent. The k_φ^0 values increased with an increasing temperature. The apparent molar volume and apparent molar adiabatic compressibility were fitted into the Redlich-Mayer equation for rational correlations to be accomplished. The negative values of E_φ^0, indicate that there is existence of weak solute-solvent interactions in all mixtures studied. The value of E_φ^0 and increase with increasing temperature showing that increases thermal agitation, resulting in sulphamethizole, sulphabenzamide, sulphaquinoxaline and sulphachloropyridizine molecules being discharged

from methanol, in this manner expanding the solution volume to a greater extent than for the pure solvent. The negative values of E_{φ}^{0} also represent the dominance of electrostriction over solvophobic interaction. The negative values of ΔV_{φ}^{0} of methanol in aqueous solution of sulphamethizole, sulphabenzamide, sulphaquinoxaline and sulphachloropyridazine are due to the decreasing solute-solvent interactions. The very small and negative values of Δk_{φ}^{0} are an indication of less compressibility than the one existing in bulk solution and decrease as temperature increase. All $\left(\partial^2 V_{\varphi}^{0} \middle/ \partial T^2\right)_{\mathrm{p}}$ values are positive for all systems. Thus, the solute methanol acts as a structure maker in aqueous solution of sulphamethizole or sulphabenzamide or sulphaquinoxaline or sulphachloropyridizine. Thus, the results from these studies can be used in flow affirmation and oil recuperation, configuration of partition procedures, selection of solvent and emanation, estimation of the dispersion of chemicals in different various ecosystems. These results can also be helpful for comprehension of the thermodynamic and transport properties related with fluid flow and heat and also in understanding the pharmacokinetics and pharmacodynamics of sulphonamide drugs.

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APPENDIX 1

Results for (methanol + water) system

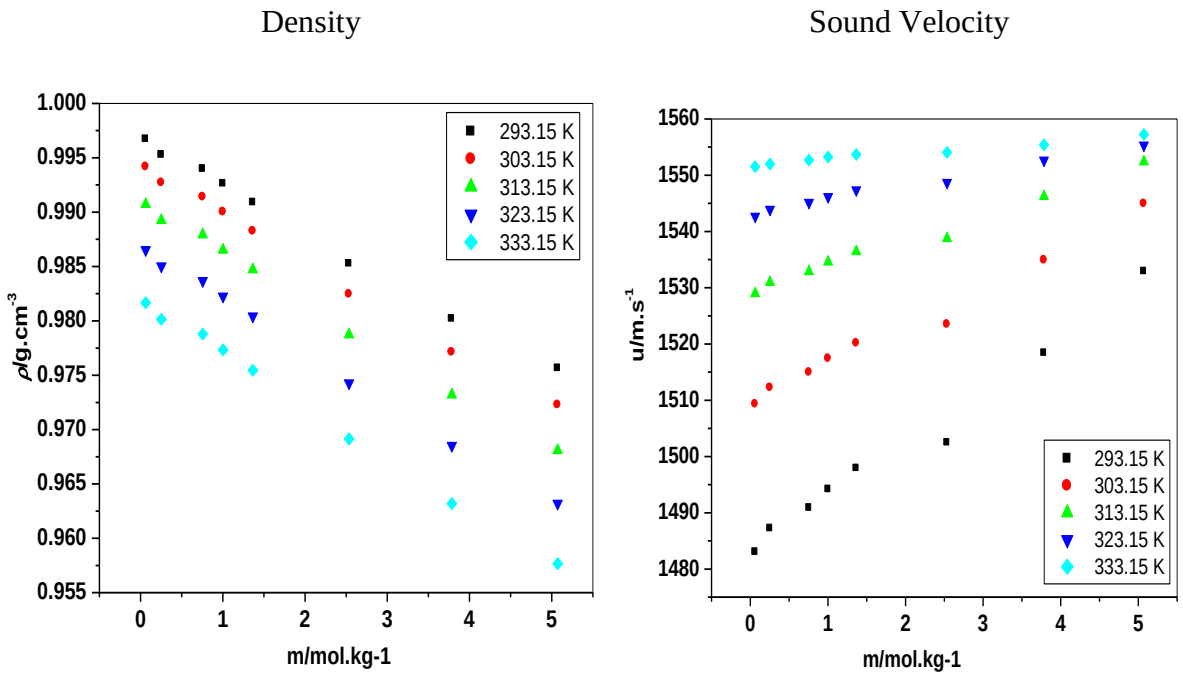
TABLE 1A

Density, ρ, sound velocity, The apparent molar volume, V_φ, and apparent molar adiabatic compressibility, k_φ, of methanol in water at (293.15, 303.15, 313.15, 323.15 and 333.15) K and at pressure p = 0.1 MPa.

M (mol^{-1}·kg^{-1})	ρ (kg.m^{-3})	u (m·s^{-1})	$10^3 V_\varphi$ (m^3·mol^{-1})	$10^{-5}\ k_\varphi$ (m^3·mol^{-1}·Pa^{-1})
		Methanol + water		
		T = 293.15 K		
0.0624	0.996719	1487.2	-4.38	17.6
0.2536	0.995267	1490.9	-1.00	17.7
0.7569	0.993970	1494.2	-0.31	17.8
1.0027	0.992611	1497.9	-0.23	17.9
1.3655	0.990881	1502.5	-0.15	18.0
2.5359	0.985256	1518.4	-0.07	18.5
3.7843	0.980187	1532.9	-0.03	19.0
5.0718	0.975639	1545.2	-0.01	19.4
		Methanol + water		
		T = 303.15 K		
0.0624	0.994167	1512	-4.60	18.0
0.2536	0.992705	1515	-1.05	18.1
0.7569	0.991393	1517.4	-0.33	18.2
1.0027	0.990016	1520.2	-0.24	18.3
1.3655	0.988248	1523.5	-0.16	18.4
2.5359	0.982440	1534.9	-0.07	18.8
3.7843	0.977114	1544.9	-0.03	19.1
5.0718	0.972272	1553	-0.02	19.4
		Methanol + water		
		T = 313.15 K		
0.0624	0.990727	1531	-4.81	18.3
0.2536	0.989250	1532.9	-1.10	18.4
0.7569	0.987920	1534.6	-0.35	18.4
1.0027	0.986521	1536.5	-0.25	18.5
1.3655	0.984719	1538.8	-0.17	18.6
2.5359	0.978740	1546	-0.08	18.9
3.7843	0.973190	1552.4	-0.04	19.1
5.0718	0.968096	1556.8	-0.02	19.3
		Methanol + water		
		T = 323.15 K		
0.0624	0.986531	1543.9	-5.01	18.4

0.2536	0.985038	1545.1	-1.14	18.5
0.7569	0.983688	1546.2	-0.36	18.5
1.0027	0.982265	1547.4	-0.26	18.6
1.3655	0.980424	1548.7	-0.18	18.7
2.5359	0.974280	1552.7	-0.08	18.9
3.7843	0.968526	1555.3	-0.04	19.1
5.0718	0.963205	1556.5	-0.02	19.2
		Methanol + water		
		T = 333.15 K		
0.0624	0.981670	1552	-5.22	18.5
0.2536	0.980153	1552.7	-1.19	18.5
0.7569	0.978782	1553.3	-0.38	18.6
1.0027	0.977331	1553.7	-0.27	18.6
1.3655	0.975451	1554.1	-0.19	18.6
2.5359	0.969143	1555.4	-0.08	18.8
3.7843	0.963194	1557.2	-0.04	19.0
5.0718	0.957664	1558.2	-0.02	19.1

Figure 1 A: Density, ρ, sound velocity, The apparent molar volume, V_{φ}, and apparent molar adiabatic compressibility, $k\varphi$, of methanol in water at (293.15, 303.15, 313.15, 323.15 and 333.15) K and at pressure p = 0.1 MPa.



Apparent molar volume Apparent molar adiabatic compressibility

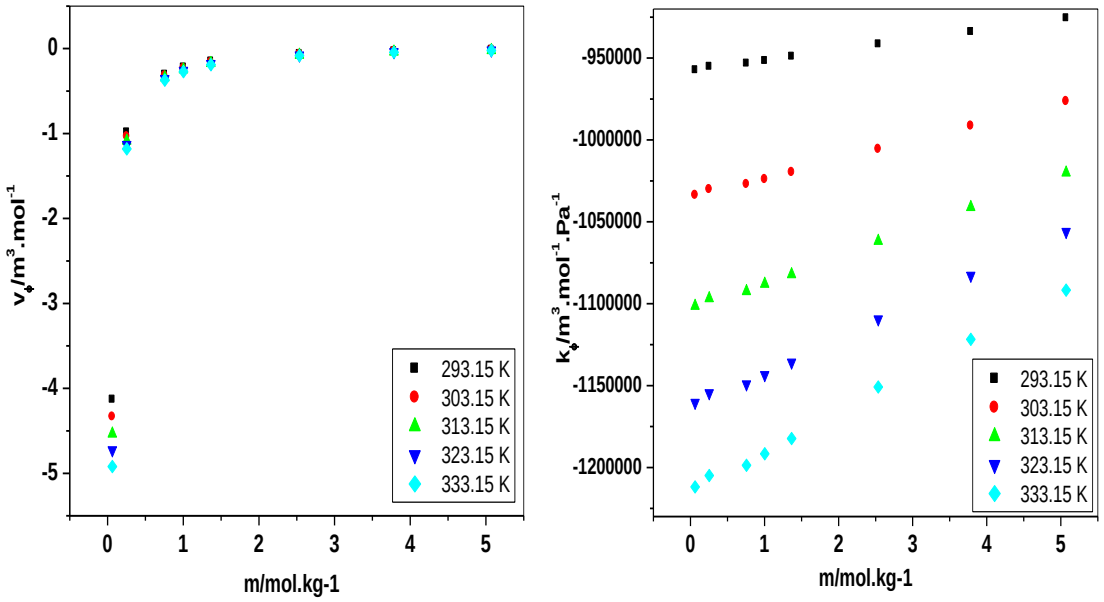


Figure 1 A: Density, ρ, sound velocity, apparent molar volume, V_φ, and apparent molar adiabatic compressibility, k_φ, of methanol in water at (293.15, 303.15, 313.15, 323.15 and 333.15) K and at pressure p = 0.1 MPa.

TABLE 2A

The limiting values of apparent molar volume, V_φ^0 and apparent adiabatic compressibility, k_φ^0 of methanol in water at (293.15, 303.15, 313.15, 323.15 and 333.15) K and at pressure p = 0.1 MPa.

T (K)	10^3 x V_φ^0 ($m^3 \cdot mol^{-1}$)	10^{-5} x k_φ^0 ($m^3 \cdot mol^{-1} \cdot Pa^{-1}$)
293.15	-2.44	17.7
303.15	-2.56	18.0
313.15	-2.68	18.3
323.15	-2.79	18.4
333.15	-2.91	18.5

APPENDIX 2

List of publications

Solute-solvent interactions of alcohols in aqueous solutions of sulphonamide derivatives at different temperatures (Communicated to RSC Advances).