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Investigation on molecular interactions of antibiotics in alcohols using volumetric and acoustic studies at different temperatures

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ABSTRACT

The density and sound velocity for pure alcohols (methanol, ethanol, iso-propanol and *n*-butanol) and molal solutions of nitroimidazoles (metronidazole (MNZ) and dimetridazole (DMZ) have been measured at different temperatures (293.15–313.15 K). Different volumetric and acoustical parameters like apparent molar volume (V^{ϕ}), partial molar volume (V^{ϕ}), apparent molar isentropic compressibility (K^{ϕ}), partial molar isentropic compressibility (K^{ϕ}), hydration number (n_H), acoustic impedance (Z) and intermolecular free length (L_f) of antibiotic solutions were calculated from the experimental values of density and sound velocity. The derived values have been used to explore the solute–solute and solute–solvent interactions. The V^{ϕ} values are positive and K^{ϕ} values are negative in both antibiotics, indicative of strong solute–solvent interactions and closely packed structure of antibiotics in alcohols. The decreasing trend of L_f with increasing antibiotic concentration shows the presence of strong intermolecular interactions in solutions.

1. Introduction

Solubility is a basic physico-chemical property that has significant applications to different processes *i.e.* biological, chemical, pharmaceutical and environmental. Careful experimentation is required for reliable solubility data and these measurements are tedious, time consuming and costly [1]. Volumetric and acoustical properties like apparent molar volume and apparent molar isentropic compressibility *etc.* of any solution can be evaluated using density and sound velocity values [2]. Volumetric properties of the mixtures of alcohols are of technological and theoretical interest.

Different types of interactions like ion–ion, solvent–solvent and ion–solvent interactions are present in the solution [3]. From the density (ρ), sound velocity and viscosity (η) of solutions, structural aspects and properties of the solutions can be characterized [4]. Hence volumetric properties give helpful information regarding nature of solute and solvent [5]. The partial molar and apparent molar volumes of solutes are used to distinguish solutes of different molar masses on the basis of their ion–ion and ion–solvent affinity and in assessing drug potency whereas isentropic compressibility factors reflects the compactness of the hydration layers around the core of the solutes [6]. Solubility results also serve to construct mathematical models that help to optimize solvent composition selection in pharmaceutical technology [1].

It has been noted that by the addition of solute, changes occur in the structure of solvent *i.e.* it may either make or break [4]. By ultrasonic velocity measurements, the molecular interactions in pure liquids, aqueous solutions and mixtures have been studied. It gives a useful and reliable tool to study the properties of solutions of amino acids, polymers *etc.* However, little work has been done for the solutions of drugs [7].

Chemical transformations can take place in a gas, liquid or solid phase but majority of reactions are carried out in liquid phase in the form of solutions [8]. Alcohol is a class of organic compounds described by one or more hydroxyl (–OH) groups attached to a carbon atom of hydrocarbon chain. These might be considered as organic imitative of water, in which a hydrogen atom has been changed by $-CH_2$ group, which may be represented by 'R' in organic structures. For example, in ethanol the alkyl group is the ethyl group, $-CH_2CH_3$ [9].

Globally, infections in gastrointestinal track by different parasites and bacteria are responsible for major morbidity and deaths. 5-Nitroimidazoles, a set of medicines, is a well-established group of antiprotozoal and antibacterial agents that have ability to reduce the development of anaerobic bacteria and certain anaerobic protozoa. The significance of imidazole is established from the fact that large number of medicines contains this moiety and several 5-nitroimidazole derivatives such as metronidazole (MNZ), dimetridazole (DMZ), ipronidazole (IPZ) and ronidazole (RNZ) have

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been used since long time, for the handling of critical cases of infections caused by protozoa and anaerobic bacteria [10]. They are placed into coccidiostat substances, but it has been reported that these compounds show mutagenic, carcinogenic and toxic properties. For this reason, their use has been prohibited as additives in feed for food-producing species. Chemical nature of drugs is essential to study their behaviour in different systems.

This study is an attempt to explore the interactions of these antibiotics with solvents and solvent–solvent interactions from volumetric and acoustical properties (apparent molar volume (V^{ϕ}), isentropic compressibility (K^{ϕ}), partial molar volume ($V^{\circ\phi}$), partial molar compressibility (K^{ϕ}), acoustic impedance (Z), hydration number (n_h) and intermolecular free length), which were evaluated from density and sound velocity of antibiotics (DMZ and MNZ) in different alcohols at different temperatures.

2. Experimental

2.1. Materials

Chemicals, MNZ, DMZ, methanol, ethanol, iso-propanol and *n*-butanol, were products of Sigma, and were used as received without any purification. All glassware was carefully washed with deionized water, cleaned and dried in oven before use. Mass fraction purity and source of chemicals used in the experiment have been given in Table 1.

2.2. Density and sound velocity measurements

Density (d) and sound velocity (u) were measured by Anton Paar DSA 5000 M with high precision vibrating tube digital density meter and ultrasound speed measuring device. The instrument has a built-in thermostat to maintain the temperature. The accuracy and repeatability of DSA 5000 M for density are 5×10^{-6} g cm^{-3} and 1×10^{-6} g cm^{-3} and that of temperature is 0.01 °C and 0.001 °C respectively. The sample density is determined by measuring the oscillation frequency of a U-shaped sample tube completely filled with the sample liquid. The principle of sound velocity measurement is based on propagation time technique. The sample is sandwiched between two piezoelectric ultrasound transducers. One transducer emits sound waves through the sample-filled cavity (frequency around 3 MHz) and the second transducer receives those waves [11]. Thus, the sound velocity is obtained by dividing the known distance between transmitter and receiver by the measured propagation time of the sound waves up to 0.5 m s^{-1}accuracy and 0.1 ms^{-1} repeatability. Density and sound velocity of pure alcohols and solutions of DMZ and MNZ of various concentrations (0.01–0.05) mol kg^{-1} in alcohols were measured at temperatures 293.15 K, 298.15 K, 303.15 K, 308.15 K and 313.15 K and at 101 kPa pressure. The weighing of solutes (antibiotics) was done by Wiggen Hauser electronic balance with a precision of ±0.001 mg. At least three readings of each composition were reproducible to ±0.005 mg and the values obtained were averaged. The standard uncertainties in molality (m), density (d), sound velocity (u_s), and temperature (T) and pressure (P) are ±0.0015 mol kg^{-1}, ±1 × 10^{-3} g cm^{-3}, ±2 m s^{-1}, ±10^{-2} K and ±5 kPa respectively. The measured densities and ultrasound speeds were utilized in determining volumetric and acoustical properties of solutions as described in the next section.

3. Results and discussion

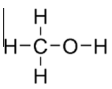
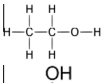
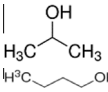
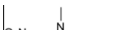
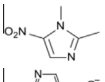
3.1. Density and sound velocity measurement of antibiotic solutions

Density and sound velocity of alcohols: methanol, ethanol, iso-propanol and *n*-butanol have been measured at different temperatures (293.15 K–313.15 K). The measured density and sound velocity values for pure alcohols have been given in Table 2. Comparison of experimental with literature values showed that measured values is in accordance with literature reported values [11–17].

Density and sound velocity for the antibiotics (DMZ and MNZ) in alcohols were measured at temperatures (293.15 K–313.15 K) using antibiotic concentration range (0.01–0.05 mol kg^{-1}). Measured density values have been given in Table 3 which show that density of antibiotic solutions decreases with increasing temperature and show an increase with increasing concentration of antibiotics in alcoholic solutions. With increasing temperatures, density decreases because increasing temperature weakens the bonds between solute and solvent in a solution making the solution less dense [2]. Density increases with increasing concentration of solute (antibiotics) in alcoholic solution which can be interpreted by the enhanced structure of solvents due to added solute (antibiotics) [18]. From values shown in the tables, it is also clear that density of MNZ in all alcoholic solutions is greater than that of DMZ because the –OH group in MNZ is responsible for greater attractive forces like H-bonding *etc.* with solvent molecules than in DMZ and hence has a more dense structure.

Sound velocity values for both antibiotics in alcoholic solutions at different temperatures (293.15–298.15) K are given in Table 6. Sound velocity decreases with increasing temperature and increases with increasing concentration of antibiotics in alcohol solutions. With increasing temperature, molecules gain kinetic energy. As the kinetic energy of molecules increases, the interactions among solute and solvent molecules become weaker. The

Table 1
Provenance and mass fraction purity of the materials studied.

Chemical names	Source	Mass fraction purity	Purification method	CAS no	Structures
Methanol	Sigma Aldrich	>0.998	Used as received	67-56-1	
Ethanol	Sigma Aldrich	>0.995	Used as received	64-17-5	
Iso-propanol	Sigma Aldrich	>0.995	Used as received	67-63-0	
n-Butanol	Sigma Aldrich	>0.994	Used as received	71-36-3	
Dimetridazole	Sigma Aldrich	>0.997	Used as received	551-92-8	
Metronidazole	Sigma Aldrich	>0.996	Used as received	443-48-1