Physico-chemical studies on binary aqueous solutions of Anti-Viral Influenza drugs

S. Punitha, R. Uvarani, A. Panneerselvam, S. Nithiyanantham

Department of Physics, Pavai Arts and Science College, Namakkal, Tamilnadu, 637018, India
Department of Physics, Thiruvalluvar Govt. Arts College, Tamilnadu, Namakkal, 637401, India
Department of Physics, Pavai Engineering College, Tamilnadu, Namakkal, 637018, India
Department of Physics, Thiru.Vi. Kalayanaundaram Govt Arts and Science College, 610003, Thiruvarur, Tamilnadu, India

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The ultrasonic velocity, density, viscosity and absorption have been measured for solution of Influenza Anti-Viral drugs (Amantadine and Oseltamivir) are presented at room temperature 303K. By taking measurements of Anti Influenza Viral drugs at 0.2, 0.4 and 0.6% concentrations of each solution. The aim of the study is to increase the solubility, stability, sweetness of drugs by the formation of complexation. The ultrasonic velocity, density and viscosity have been measured at 2MHz for the aqueous solutions of (i) Influenza Anti-Viral Drugs + HPMC (Hydroxy Propyl Methyl Cellulose), Lactose and CaCl₂ (Calcium Chloride at different concentrations at a temperature 303K. The acoustical parameters such as adiabatic compressibility (β), intermolecular free length (L₀), internal pressure (α), Rao’s constant (R), relaxation time (τ), acoustical impedance (Zₐ), absorption coefficient (α/β²), free volume (Vᵢ), cohesive energy and solvation number (Sn) have been computed. These properties are attributed to solute-solvent interactions through hydrogen bonding, segment-segment interaction, molecular association, polymer-solvent interaction, polymer-polymer interaction and etc. The total absorption can be considered as the sum of contributions from solute-solvent interactions. These results are further supported by FTIR studies.

1. Introduction

The ultrasonic study of an aqueous mixture is important in understanding the nature of molecular interactions. The biological activity of drug molecules and the activation energy of the metabolic process basically depend on the type and strength of the inter-molecular interactions (Bedare et al., 2014). Interaction of drugs with different additives was carried out in order to increase their properties and applications; indeed, it was found so (Dileep and Malik, 2017; Dileep et al., 2018a; 2018b; 2018c). Amantadine is an antiviral medication used to prevent or treat certain influenza infections; Amantadine shows potential for use as a safe alternative/augmenting agent for treating children with neuropsychiatric and various other disorders (Hosenbocus and Chahal, 2013). Oseltamivir is an antiviral medication that blocks the actions of influenza virus types A and B in our body. Oseltamivir is an orally administered antiviral medication that selectively inhibits the influenza neuraminidase enzymes that are essential for viral replication. Oseltamivir is suitable for use in diverse patient populations, which may include young children and elderly patients, various ethnic groups and those with renal or hepatic impairment (Brian and Davies, 2010). Now a day’s Ultrasonic investigations is employed in a wide range of applications in medicine, biology, industry, material science, agriculture, oceanography, sonochemistry due to its non-destructive nature (Blitz, 1963; Suslick, 1988; Mason, 1990; Naik et al., 2015; Carnemic et al., 1999; Kruger et al., 1999; Masuelli, 2018). Polymers are one of the most essential products which ambiances us in every gait of life HPMC is a polysaccharide prepared from cellulose (Arumugam et al., 1998). It contains both methyl and hydroxy propyl substitutes. In the present study, HPMC has been chosen as polymer, as they have many pharmaceutical and biomedical applications (Nithiyanantham et al., 2012). A new approach for escalating a drug–excipients mixed coat with highly water-soluble has been investigated. Studies reveal that incorporation of hydrophilic substances such as HPMC, Lactose, CaCl₂ with drugs itself considerably increase the release rates. An important research area involves the development of sustained delivery systems, which are designed to control the release of drugs at a special rate over a defined time period.
### Table 1

The measured parameters Ultrasonic velocity (U), density (ρ), viscosity (η) and the derived parameters adiabatic compressibility (β), free length (L), internal pressure (π), Rao's constant (R), absorption coefficient (α/β²), free volume (Vf), cohesive energy (CE), relaxation time (τ), acoustical impedance (Za) and salvation number (Sn) for Amantadine + HPMC, Oseltamivir + HPMC, Lacotex, Oseltamivir + Lacotex and Amantadine + CaCl₂, Oseltamir + CaCl₂ in aqueous solution at 303K.

| Conc/% | Amantadine + HPMC | Lactose + CaCl₂ | Amantadine + Lacotex | Amantadine | Amantadine + CaCl₂ | Oseltamivir + HPMC | Oseltamivir + Lacotex | Oseltamir + CaCl₂ |
|--------|--------------------|----------------|----------------------|-----------|--------------------|--------------------|--------------------|------------------|
| U m/s  | 1531               | 1010           | 0.912                | 4.224     | 0.410              | 0.883              | 1.462              | 1.012            | 0.011            | 1.123              | 5.135             | 1.546              |
| P kg/m³ | 1531               | 1010           | 0.912                | 4.224     | 0.410              | 0.883              | 1.462              | 1.012            | 0.011            | 1.123              | 5.135             | 1.546              |
| η x 10⁻³ Num² | 1531               | 1010           | 0.912                | 4.224     | 0.410              | 0.883              | 1.462              | 1.012            | 0.011            | 1.123              | 5.135             | 1.546              |
| β x 10⁻¹² N⁻¹ m² | 1531               | 1010           | 0.912                | 4.224     | 0.410              | 0.883              | 1.462              | 1.012            | 0.011            | 1.123              | 5.135             | 1.546              |
| LfÅ | 1531               | 1010           | 0.912                | 4.224     | 0.410              | 0.883              | 1.462              | 1.012            | 0.011            | 1.123              | 5.135             | 1.546              |
| α x 10⁻¹ⁱ Npm² | 1531               | 1010           | 0.912                | 4.224     | 0.410              | 0.883              | 1.462              | 1.012            | 0.011            | 1.123              | 5.135             | 1.546              |
| Vf m³/mol | 1531               | 1010           | 0.912                | 4.224     | 0.410              | 0.883              | 1.462              | 1.012            | 0.011            | 1.123              | 5.135             | 1.546              |
| CE x 10⁸ kJmol⁻¹ | 1531               | 1010           | 0.912                | 4.224     | 0.410              | 0.883              | 1.462              | 1.012            | 0.011            | 1.123              | 5.135             | 1.546              |
| τ x 10⁻¹³ s | 1531               | 1010           | 0.912                | 4.224     | 0.410              | 0.883              | 1.462              | 1.012            | 0.011            | 1.123              | 5.135             | 1.546              |
| Za x 10⁶ kgm²/s³ | 1531               | 1010           | 0.912                | 4.224     | 0.410              | 0.883              | 1.462              | 1.012            | 0.011            | 1.123              | 5.135             | 1.546              |
| Sn | 1531               | 1010           | 0.912                | 4.224     | 0.410              | 0.883              | 1.462              | 1.012            | 0.011            | 1.123              | 5.135             | 1.546              |
as well as patient compliance, especially where infants, children and elderly are concerned.

In order to achieve more pleasant dosage forms, various masking techniques have been described in the literature (Shouand and Chen, 2002; Yuan et al., 2016). Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include physical and chemical modifications of drug and other methods like particle size reduction, crystal engineering, salt formation, solid dispersion, use of surfactant, complexation and etc. The simplest method is to add flavors or sweeteners. However, in most of the cases, these are rather limited and may not be effective enough to mask the unpleasant taste of some drugs. A number of more useful approaches have been tried, including capsule formulations, coating with water-soluble polymers, microencapsulation with various polymers (Loftsson and Masson, 2001; Nithiyanantham and Palaniappan, 2010), and chemical modification such as turning drugs into their milk-toast prodrugs without any reduction in bioavailability.

2. Materials and methods

The pure samples of these polymers and carbohydrate with a purity of 99.5 % are obtained from Madras scientific Chemicals, Salem. The drug gift samples are obtained from Sun plasma, Mumbai, India. The ultrasonic velocity and absorption studies are undertaken in the aqueous solutions of (i) Influenza anti-viral drugs (Amantadine and Oseltamivir) + HPMC, Lactose and CaCl₂ with a view to understand the nature of interaction between the two different solutes at 303K. Double distilled water is used in the preparation of experimental solution. For this different dissolved ultrasonic velocities of solutions were measured using a single frequency continuous wave ultrasonic interferometer (Model F81, Mittal Enterprises) to an accuracy of ±0.05% at a frequency of 2MHz at 303K. The temperature of the samples were maintained constant to an accuracy of ±0.1K using a thermostatically controlled digital water bath. This is the principle based on the reflection from the bottom and top of the cell. The reflection and the conversion of mechanical energy converted into electrical energy with help of piezo electric crystal (transducer) situated at the bottom of the ultrasonic cell. This will produce the standard wave pattern and it depends on the nature of liquids hold in the cell. The densities of the solutions were measured using a specific gravity bottle with an accuracy of ±0.01 kgm⁻³. The viscosity was measured using Ostwald’s viscometer to an accuracy of ±0.2%. The FTIR spectra were collected for these samples using Fourier Transform Infra-Red Spectrometer. Model: Spectrum RX, Perkin Elmer. All spectra were collected in the range (4000-400cm⁻¹). The KBr technique was used to prepare the samples for IR measurements.

3. Calculation

3.1. Physical parameters

Thermodynamic parameters such as adiabatic compressibility (β), intermolecular free length (Lₐ), internal pressure (π), acoustic impedance (z) and Solvation number (Sₙ) were calculated from empirical Jacobson’s relations (Nithiyanantham and Palaniappan, 2010; Kazafi and Ansari, 2011).

(i) Adiabatic compressibility

\[ \beta = 1/a^2 ρ \]  

has been calculated from the u-ultrasonic velocity and ρ-density of the medium using the Newton –Laplace equation.

(ii) Intermolecular free length

\[ L_α = K_f \beta^{1/2} \]  

Where K_f is the temperature dependent constant known as Jacobson’s constant (K_f = 2.131 × 10⁻⁶), and β is the adiabatic compressibility

(iii) Internal pressure

\[ π_i = bR/T [K_π u^{12}]ρ^{2/3} M^{7/6} \]  

Where, b stands for cubic packing, which is assumed to be 2 for all liquids, T-absolute temperature in Kelvin, Where Meff is the effective molecular weight of the mixture (M_eff = \sum m_i x_i where m_i and x_i are the molecular weight and mole fraction of individual constituents, respectively K is a temperature independent constant which is equal to 4.281 × 10⁹ (Nithiyanantham and Palaniappan, 2014) for all liquids, R is the universal gas constant, \( η \) -viscosity of the solution).

(iv) Rao's constant

\[ R_o = (M/ρ) (u)^{1/3} \]  

(v) Relaxation time

\[ τ = 4/3πη \]  

(vi) Acoustic impedance

\[ za = ρ u \]  

(vii) Absorption coefficient

\[ α/f^2 = (8π^2η/3π^2r^2) \]  

(viii) Free Volume

\[ V_f = (M_eff ρ/κ) \]  

(ix) Cohesive energy

\[ CE = V_f π_i \]  

(x) Solvation number

\[ S_n = M_2/M_1 [1-(π/π_0))][((100-x)/x)] \]  

Where M_1, M_2 are the molecular weight of the solvent and solute, β and π₀ are the adiabatic compressibility of solution and solvent.

4. Results and discussions

4.1. Influenza anti-viral drugs (Amantadine and Oseltamivir) + HPMC, Lactose and CaCl₂

Using the measured values of ultrasonic velocity, density and viscosity of the solutions other acoustical parameters, viz., adiabatic...
In density, viscosity gradually increases with the increase in concentration. From the same Table 1, the absorption coefficient (7) values are found to decrease on the addition of solutes almost in all the system of studies. Ultrasonic relaxation processes in polymer solutions may result from viscoelasticity, polymer-solvent interaction and polymer-polymer interaction.

From the polar HPMC, Lactose and CaCl₂ the orientation of polar molecules in the direction of the field is faster. When solute is added to the solvent (HPMC, Lactose and CaCl₂ with 1% drugs), the dipole moment of this solute may cause the solvent molecule to orient in an orderly manner than before, which may cause the decrease in absorption of the solvent on adding solute. Dilute solutions contain isolated macromolecules of coiled conformation in the solvent, whose molecules are oriented near macromolecules.

When a solute is dissolved in aqueous carbohydrate or polymer solution, it can have two effects: (i) the solute act as acceptors and they can complete with protons for the lone pair of electrons on the oxygen. This leads to the formation of solution sheath around the new solute and the polymer. The equilibrium between the two structural forms in water is distributed, which leads to a change in absorption in the aqueous HPMC, Lactose and CaCl₂ with 1% drug solution (Geetha and Rakkappan, 2005). The concept of free volume (8) is a generalized aspect of the idea that its neighbors in a cell encode each molecule. The free volume is broadly defined as the averages volume in which the center of the molecule can move inside the hypothetical cell due to the repulsion on the surrounding molecules.

Solvation number (Table 1) decreases and then increases with an increase in solute concentration. The values of Sn correspond to the number of solvent molecules in the primary solvation sheaths of the ions. On account of electrostriction molecule, the solvation sheath will be less compressible than that in the bulk of the solution when an external pressure is applied. The compressibility of solvent molecule near but not in the primary solvation sheath is the same as those of pure solvent molecules than that of actual primary solvation numbers. The higher values of solvation number (10) suggest a considerable dissociation of solute molecules. In some systems, solvation number increases with solute concentration, because the solutes may have two lone pairs for the interaction with the solvent molecule. The resultant values of Sn are decided by the type of interaction occurring in the solution. The decrease of Sn with the concentration indicates that solute-solute interaction is more powerful than solute-solvent interaction. The increase of Sn with solute concentration indicates that solute-solute interaction is more powerful than solute-solvent interaction in some systems.

The solute - water interaction due to hydrogen bonding is a major source ultrasonic relaxation. The mechanism should produce a linear increase in density and ultrasonic velocity and absorption with increasing concentration. The decrease of cohesive energy and increase is due to the influence of electrostatic field of the ions on the surrounding solvent molecules (Majumdar et al., 1980). It may be explained on the basis of close-packing of ionic head groups in the solute resulting in an increase in ionic repulsion and finally internal pressure decreases in some systems. When the size of the solute increases, the repulsion also increases, thereby a decrease in the value of β occurs. The reduction in π may be due to the loosening of cohesive forces (9) which leads to breaking up the structure of the solvent (Kazafi and Ansari, 2011; Nii and Ishii, 2005; Savjani et al., 2012; Shipra and Oza, 2002).

The specific acoustic impedance (6) increases with an increase in solute concentration (Table 1). It can be explained on the basis of solute-solvent interaction between the intramolecular distance leaving a relatively wider gap between the molecules and thus becoming the main cause of impediments to the propagation of ultrasonic waves. The non-linear variation of Rao's constant (Ra) (4) and the gradual increase in acoustic impedance (Za) (6) with increase in concentration predict the strong intermolecular association complexes between the molecule of Influenza Anti-Viral drugs (HPMC, Lactose and CaCl₂) molecules. The increase of HPMC, Lactose and CaCl₂ concentration is accompanied by an increase of relaxation time (5).

From the same Table 1, the absorption coefficient (7) values are found to decrease on the addition of solutes almost in all the system of studies. Ultrasonic relaxation processes in polymer solutions may result from viscoelasticity, polymer-solvent interaction and polymer-polymer interaction.

From the polar HPMC, Lactose and CaCl₂ the orientation of polar molecules in the direction of the field is faster. When solute is added to the solvent (HPMC, Lactose and CaCl₂ with 1% drugs), the dipole moment of this solute may cause the solvent molecule to orient in an orderly manner than before, which may cause the decrease in absorption of the solvent on adding solute. Dilute solutions contain isolated macromolecules of coiled conformation in the solvent, whose molecules are oriented near macromolecules.

When a solute is dissolved in aqueous carbohydrate or polymer solution, it can have two effects: (i) the solute act as acceptors and they can complete with protons for the lone pair of electrons on the oxygen. This leads to the formation of solution sheath around the new solute and the polymer. The equilibrium between the two structural forms in water is distributed, which leads to a change in absorption in the aqueous HPMC, Lactose and CaCl₂ with 1% drug solution (Geetha and Rakkappan, 2005). The concept of free volume (8) is a generalized aspect of the idea that its neighbors in a cell encode each molecule. The free volume is broadly defined as the averages volume in which the center of the molecule can move inside the hypothetical cell due to the repulsion on the surrounding molecules.

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The solute - water interaction due to hydrogen bonding is a major source ultrasonic relaxation. The mechanism should produce a linear increase in density and ultrasonic velocity and absorption with increasing concentration. The decrease of cohesive energy and increase
of relaxation time clearly confirm the complex formation around the HPMC, Lactose and CaCl2 with 1% drugs molecule which leads to a decrease in free water component.

4.2. FTIR spectra for binary mixture of influenza anti-viral drugs with HPMC, Lactose, CaCl2

The characteristics peaks of Influenza anti-viral drugs with excipients of HPMC shows the broad spectrum of strong $\nu$(OH) band. The $\nu$(OH) band of 3341 cm$^{-1}$ in Amantadine drug is shifted to 3382 cm$^{-1}$ in the mixture of HPMC, but in the mixture of Lactose and CaCl2 it was about 3199 cm$^{-1}$ and 3303 cm$^{-1}$ and it may have interaction with the carboxyl group is displayed in Fig. 6.

The wave numbers observed in the region of 2920 cm$^{-1}$ was assigned to C–H stretching vibration and it was shifted to 2711 cm$^{-1}$, 2984 cm$^{-1}$, 2970 cm$^{-1}$Amantadine(HPMC + Lactose + CaCl2). The band arising at 1084 cm$^{-1}$ due to C–N stretching of aliphatic amines was shifted to 1085 cm$^{-1}$ in Amantadine + HPMC, Amantadine + Lactose. The IR spectrum of the entire mixture component can be shown that the interaction between two different molecules is not much more influenced. However, we can discuss the interaction in the form of hydrogen bonding. Similarly in Fig. 7 (a, b, c and d) the $\nu$(OH) band of 3351 cm$^{-1}$ was observed in Oseltamivir. The change in OH stretching was not observed in Oseltamivir + HPMC but small changes were observed in Oseltamivir + Lactose and Oseltamivir + CaCl2 bands at 3345 cm$^{-1}$ and 3408 cm$^{-1}$.

The observed level of C–H stretching vibration of 2934 cm$^{-1}$ was shifted to 2932 cm$^{-1}$ of Oseltamivir + HPMC and Oseltamivir + Lactose and 2936 cm$^{-1}$ of Oseltamivir + CaCl2. The strong bond of C=O stretch in Oseltamivir at 1719 cm$^{-1}$ was observed. There was no change observed in Oseltamivir + Lactose and Oseltamivir + CaCl2. Similarly the mixture also have the interaction with amino group and C=O group.

5. Conclusion

The ultrasonic velocity and absorption data for the aqueous solutions of (i) Influenza Anti-Viral Drugs/HPMC, (ii) Influenza Anti-Viral Drugs/Lactose and (iii) Influenza Anti-Viral Drugs/CaCl2 the binders HPMC, Lactose, CaCl2 enhance their solubility, stability and in vitro activity and it may be useful to enhance the pharmaceutical applications. Formation of complex with side chain of drugs is confirmed by FTIR studies for all
the above samples. Thus it can be concluded that experimental data and other acoustical calculations of these systems (Anti Influenza Viral Drugs + HPMC, Lactose and CaCl2) shows that the solute-solvent interaction through hydrogen bonding exists in lower concentrations and solute-solute interaction may be possible due to complex formation in higher concentration. Thus above results could imply greater ability of strong interaction is between Amantadine + HPMC than other binary mixtures. In brief the solute-solvent interactions through hydrogen bonding, segment-segment interaction, molecular association, polymer-solvent interaction, polymer-polymer interaction and etc.

Declarations

Author contribution statement

S Punitha: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data. R Uvarani: Analyzed and interpreted the data; Wrote the paper. A Panneerselvam: Performed the experiments; Contributed reagents, materials, analysis tools or data. Nithiyanantham Subramanian: Conceived and designed the experiments.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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