Research Article

Ion-Solvent Interaction of Cobalt Complexes of Levofloxacin and their Pharmaceutical Study

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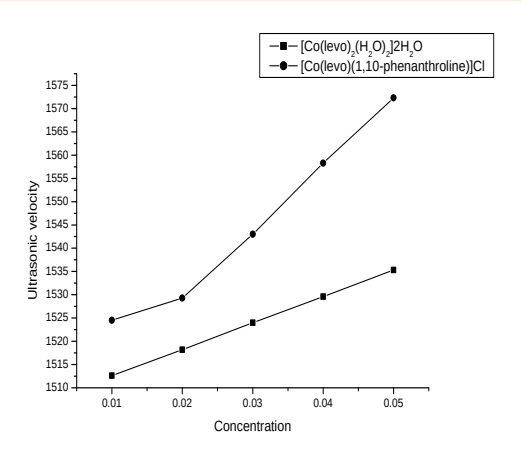
Abstract

The acoustical parameters such as sound velocity(U), adiabatic compressibility(β),acoustic impedance(Z), intermolecular free length(L_f), hydration number(n_H) of cobalt complex of levofloxacin and its complex with 1.10-phenanthroline were measured and screened for antibacterial activity against Escherichia Coli bacteria. Acoustical and volumetric properties for aqueous solutions of cobalt complexes of levofloxacin have been discussed in the light of ion-solvent interaction. Antibacterial studies of these complexes have been carried out by observing minimum inhibitory concentration (MIC) and zone of inhibition against Escherichia coli bacteria. These measurements indicate higher antibacterial activity of ternary complex of cobalt compared to normal drug.

Keywords: Ultrasonic velocity, acoustical impedance, molecular interaction, antibacterial activity, MIC.



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Introduction

A systematic knowledge of solution behavior of drugs is of great importance in order to understand their physiological action[1]. Ultrasonic studies on aqueous solution of non electrolytes in water rich region are extensively studied[2-9]. Most of the drugs are organic molecules with both hydrophobic and hydrophilic groups which are responsible for their acidic basic or amphoteric behaviors. Pharmacological properties of drugs are highly dependent on solution behavior[10]. The variations of ultrasonic velocity with concentration of aqueous solution of organic solutes[11-13] have been observed. This behavior has been attributed to the modification or stabilization of hydrogen bonded structure of water by organic solutes. But few have been reported the interaction of drugs and their metal complexes[14].

Levofloxacin, (S)-9- fluoro-3-methyl -10- (4- methyl piperazin -1-yl) - 7-oxo-2,3-dihydro-7H-pyrido [1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate (Figure 1) is a quinolone synthetic antibiotic that stops multiplication of bacteria by preventing the reproduction and repair of their genetic material DNA. It is used for testing infections of the sinuses, skin, lungs, ears, airways, bones and joints caused by susceptible bacteria.

It has been reported that metal complexation with quinolone molecules play an important role in their biological activities[15-16]. Patel et. al [17] have shown the antibacterial activities and DNA interactions of ternary copper (II) complex of levofloxacin and phenanthroline derivatives. The ultrasonic parameters are carried on Escherichia Coli grown in nutrient growth at 37^0c[18]. The binding of Mg^{2+},Ca^{2+},Sr^{2+} and Ba^{2+} ions to calf thymus DNA in solutions

has been investigated by ultrasonic velocity and density[19]. Ramteke et. al [20] have studied the ultrasonic velocity and density of substituted thiocarbamidoacetophenone and its Co(II), Cr(III) complexes in ethanol and dioxane solvents.

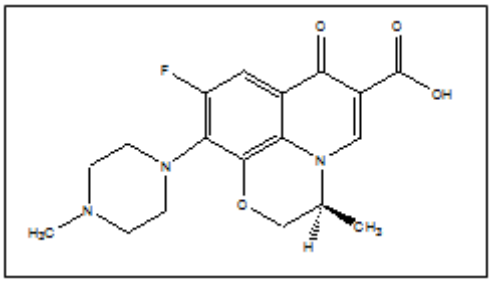

Figure 1 chemical Structure of levofloxacin

The present paper represents the ion-solvent interactions in aqueous solutions of cobalt, complexes of levofloxacin and its ternary complexes with nitrogen donor ligand (1, 10-phenanthroline) at temperature 308.15K. The examination of their antimicrobial activities against bacterial species reveals the advantages of such complexes.

Experimental

The hydrated salt $CoCl_2$ $6H_2O$ was Anal R grade. Levofloxacin were obtained from a local pharmaceutical company. Water used in this study was doubled distilled water prepared by distilling water over alkaline potassium permanganate in all glass distillation flasks. All the complexes were prepared [21-22]. and characterized by elemental analysis and spectroscopic methods. The ultrasonic velocity was measured by single crystal interferometer (Mittal, model-81) operating at a frequency of 2MHz. The temperature was maintained constant at 308.05K in a thermostat. The density of solutions was determined accurately using 10ml specific gravity bottle and electronic balance of accuracy (±0.1 mg).

Antibacterial activities of ligands and their metal complexes were investigated by paper diffusion method[23] against a particular bacterial i.e. Escherichia coli. The nutrient paper (Whatmann No-1) was used. The filter paper was soaked in aqueous solution of ligand as well as metal complexes dried and then placed in Petridis sealed with test organism. The plates are incubated for 24 hours at 37^0c inside the incubator and the inhibition zone around each disc was measured in mm.

Theory

Using the measured data the following parameters have been calculated using the standard relations,

$$U = (\beta d)^{-1/2}$$

Adiabatic compressibility, $\beta = d^{-1}U^{-2}$

Intermolecular free length, $L_f = K_j \beta^{1/2}$

Where, K_j is Jacobson constant = 2.0965×10^{-6}

Specific acoustic impedance, $Z = Ud$

Hydration number, $$n_H = \frac{n_1}{n_2}\left[1-\left(\beta-\beta^0\right)\right]$$

Where, β and β^{o} are adiabatic compressibility of solution and solvent respectively.
n_1 and n_2 are number of moles of solvent and solute respectively

Result and Discussion

The proposed structures of cobalt(II) complexes of levofloxacin are shown in **Figure 2**.

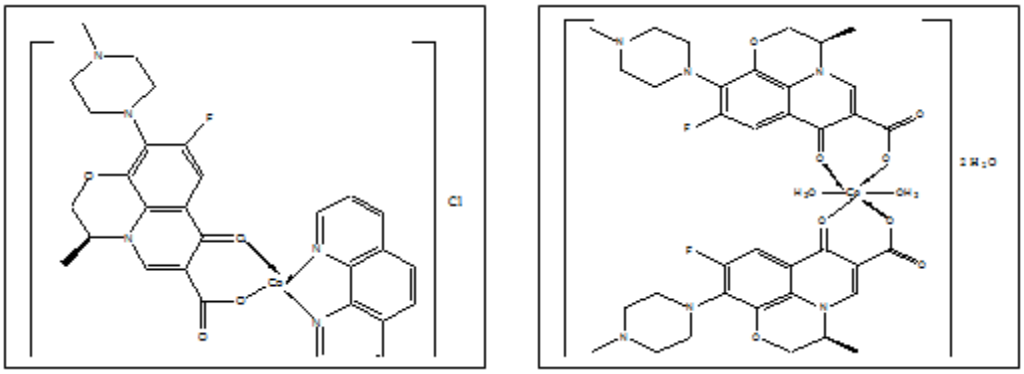

Figure 2 Proposed structures of cobalt(II) complexes of levofloxacin

Ultrasonic investigations have been carried out on aqueous solutions of cobalt complexes at 308.15K varying concentration from 0.01M to 0.05M to investigate the ion-solvent interactions. The experimental value of density (d), ultrasonic velocity (U), adiabatic compressibility (β), acoustic impedance (Z), intermolecular free length (L_f) and hydration number (n_H) of Co (II) complexes of levofloxacin and its ternary complexes with 1,10-phenanthroline in aqueous medium at 308.05K are tabulated in Table-1. Density is a measure of ion-solvent interaction. Increase in density with concentration results the increase in solvent-solvent and ion- solvent interactions. In other words it may be interpreted to the structure maker of water due to the added solute. Similarly decrease in density indicates the lesser magnitude of solute-solvent and solvent- solvent interaction indicating structure breaker of the solvent. The increase in density with increase in concentration is observed in $[Co(levo)_2(H_2O)_2]2H_2O$ and [Co(levo)(1,10-phenanthroline)]Cl (Table-1).

Table-1 Acoustical parameters of $[Co(levo)_2(H_2O)_2]2H_2O$, [Co(levo)(1,10-phenanthroline)]Cl, complexes in water at 308.15K

Concentration (c) mol dm^{-3}	Density (d) $x10^3$ kgm^{-3}	Ultrasonic velocity (U) $msec^{-1}$	Adiabatic compressibility (β) x $10^{-7}m^2N^{-1}$	Acoustic Impedance (Z) $x10^{-3}$ $kg\ m^2s^{-1}$	Intermolecular free length (L_f) $x10^{-9}$ m	hydration number (n_H)
$[Co(levo)_2(H_2O)_2]\ 2H_2O$						
0.0098	994.91	1512.6	4.3931	1504.8	1.3896	24.7764
0.0196	997.72	1518.2	4.3485	1514.7	1.3825	40.3736
0.0293	1000.6	1524.0	4.3030	1524.9	1.3752	45.9016
0.0389	1003.4	1529.6	4.2596	1534.8	1.3683	48.0053
0.0484	1005.3	1535.3	4.2201	1543.4	1.3619	48.2513

[Co(levo)(1,10-phenanthroline)]Cl						
0.0099	993.18	1524.5	4.3326	1513.9	1.3710	61.8845
0.0197	995.94	1529.3	4.2934	1523.0	1.3737	74.7670
0.0294	998.70	1543.0	4.2056	1540.9	1.3596	86.5824
0.0390	1001.5	1558.3	4.1120	1560.6	1.3444	94.1314
0.0487	1004.3	1572.3	4.0278	1579.1	1.3305	95.4547

In these complexes of levofloxacin the value of ultrasonic velocity increases with increase in concentration of the complex shown in Figure 3. The increasing trend suggests a moderately strong associative nature in which the complex molecules are surrounded by water molecules. It is also attributed to the formation of hydrogen-bonding between the complexes and water molecules.

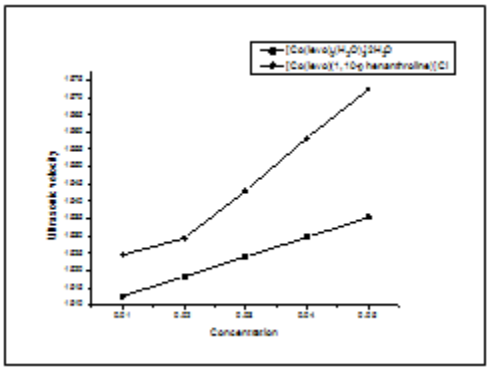

Figure 3 Variation of ultrasonic velocity (U) with concentration for $[Co(levo)_2(H_2O)_2]2H_2O$, [Co(levo)(1,10-phenanthroline)]Cl complexes in water at 308.15K

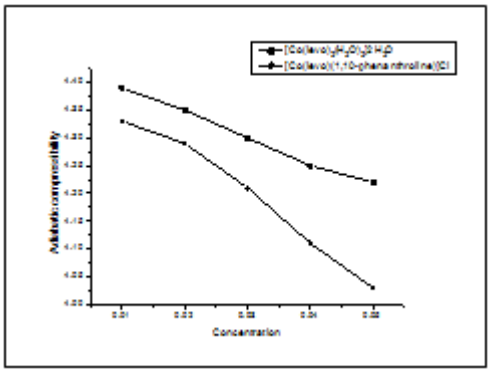

Figure 4 Variation of ultrasonic velocity (β) with concentration for $[Co(levo)_2(H_2O)_2]2H_2O$, [Co(levo)(1,10-phenanthroline)]Cl complexes in water at 308.15K

The adiabatic compressibility (β) calculated from ultrasonic velocity is a measure of intermolecular association. In the aqueous solutions of $[Co(levo)_2(H_2O)_2]2H_2O$ and [Co(levo)(1,10-phenanthroline)]Cl the decrease in β values with concentration are given in Figure 4. The increase in ultrasonic velocity and decrease in β were attributed to the formation of hydrogen bonding between solute and water molecules. The large decrease in β value in aqueous solution of [Co(levo)(1,10-phenanthroline)]Cl complex suggest the increase of ion-solvent interaction due to formation of relatively stronger hydrogen bonding compared to other complex.

Acoustic impedance (Z) is found to increase in $[Co(levo)_2(H_2O)_2]2H_2O$ and [Co(levo)(1,10-phenanthroline)]Cl with increase in the molar concentrations of the complexes. The higher impedance of [Co(levo)(1,10-phenanthroline)]Cl indicates the presence of bulkier solvated ion due to ion-solvent which restrict the free flow of solvent molecules.

Intermolecular free length (L_f) denotes the magnitude of either ion-ion, ion-solvent interaction or both of the systems. The value of L_f for all the concentrations decrease in the aqueous solution of $[Co(levo)_2(H_2O)_2]2H_2O$, [Co(levo)(1,10-phenanthroline)]Cl. The decrease in L_f value with increase in concentration of $[Co(levo)_2(H_2O)_2]2H_2O$ and [Co(levo)(1,10-phenanthroline)]Cl indicates a significant molecular association.

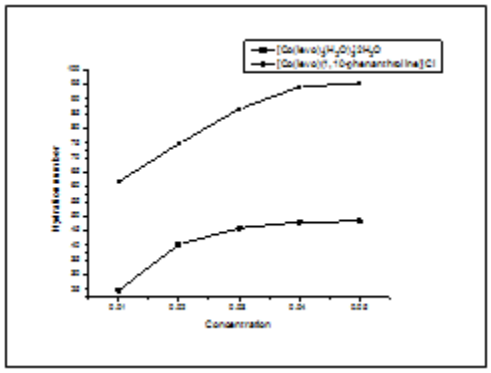

Figure 5 Variation of ultrasonic velocity (n_H) with concentration for $[Co(levo)_2(H_2O)_2]2H_2O$, [Co(levo)(1,10-phenanthroline)]Cl complexes in water at 308.15K

The molecular interaction between the solute and water molecules present in the systems can be explained in terms as hydration number (n_H). In both the systems the hydration number increases with increasing concentration (Figure 5). The positive value of hydration number indicates an appreciable solvation of solute. This is an added support for the structure intensifying properties of the solute as well as the presence of appreciable interaction between the solute and water molecules. From Table 1 it is observed that the value of hydration number is found to increase with increase in the concentration and of $[Co(levo)_2(H_2O)_2]2H_2O$, [Co(levo)(1,10-phenanthroline)]Cl. The decrease behavior of n_H has shown that the strength of interaction gets weakened in between the solute and solvent molecules and maximum n_H value for aqueous solution of [Co(levo)(1,10-phenanthroline)]Cl shows the presence of strong ion-solvent interactions.

Antibacterial study

The study of antibacterial activities of metal complexes exhibit appreciable antibacterial activities as reported by different researchers[24-26].

It is possible to select antibiotic for the inhibition of bacterial growth from the knowledge of the susceptibility of the infecting organism. Antibacterial behavior is studied for two different complexes of Co (II) against Escherichia Coli bacteria.

Figure 6,7 and 8 represent the zone size as observed for levofloxacin, $[Co(levo)_2(H_2O)_2]2H_2O$ and [Co(levo)(1,10-phenanthroline)]Cl respectively. These were susceptible to levofloxacin at 100,500 and 1000 µg/ml concentrations.

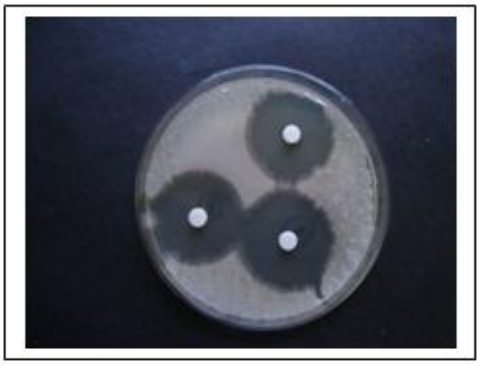

Figure 6 zone size of levofloxacin drug against the organism E. Coli

Figure 7 zone size of $[Co(levo)_2(H_2O)_2]2H_2O$ complex against the organism E. Coli

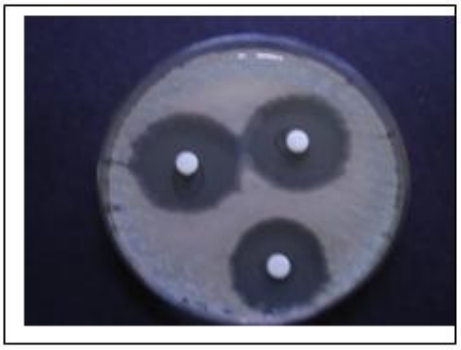

Figure 8 zone size of [Co(levo)(1,10-phenanthroline)]Cl complex against the organism E. Coli

Table 2 Zone size around each disc at 100, 500 and 1000 µg/ml for levofloxacin and its metal complexes

Ligand and metal complexes	Zone size		
	100 µg/ml	500 µg/ml	1000µg/ml
Levofloxacin(control)	32mm	32mm	34mm
$[Co(levo)_2(H_2O)_2]2H_2O$ (2:1)	27mm	30mm	32mm
[Co(levo)(1,10-phenanthroline)]Cl (1:1)	24mm	29mm	32mm

Antibacterial activity of $[Co(levo)_2(H_2O)_2]2H_2O$ complex as shown in **Table 2** reveals that at 100 µg/ml concentration, the activity of the complex is increased towards Escherichia Coli while the organism susceptibility has not been affected by cobalt complexion at higher concentration. [Co(levo)(1,10-phenanthroline)]Cl was more active at 100 µg/ml but less reactive at 500 µg/ml and it was resistant at 1000 µg/ml. The result further reveals that formation of ternary complex containing Co(II) ion results an increase in antibacterial activities as compared to levofloxacin and $[Co(levo)_2(H_2O)_2]2H_2O$ complex. The enhanced antibacterial activities can be explained on the basis of over tone concept and chelation theory[27]. Such enhancement may be due to an increase in cell permeability of the metal conjugates which allowed for the intracellular drug accumulation. It is also likely that the intracellular reduction of these complexes may lead to higher cytoplasmic concentration of metal species which prove lethal for bacteria.

Conclusions

Ultrasonic study for all metal complexes in aqueous solution at 308.15 K confirmed the presence of strong ion-solvent interaction in [Co(levo)(1,10-phenanthroline)]Cl complex and exists in the order,

$$[Co(levo)(1,10\text{-phenanthroline})]Cl > [Co(levo)_2(H_2O)_2]2H_2O$$

So, ion-solvent interactions are greatly enhanced by chelated complexes. So the nature of ligand plays vital role in determining interactions in solutions. All the metal complexes are found to have appreciable antibacterial activity against bacterial strain; however antibacterial activity is enhanced by chelation in case of cobalt complexes to some extent and follows the order,

$$[Co(levo)(1,10\text{-phenanthroline})]Cl > [Co(levo)_2(H_2O)_2]2H_2O > \text{levofloxacin}$$

So, [Co(levo)(1,10-phenanthroline)]Cl is a better antibacterial agent compared to antibacterial drug levofloxacin.

Acknowledgement

The authors are thankful to PG Dept. of Chemistry, Ravenshaw University for providing facilities to carry out this work.

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Publication History
Received 02nd July 2014
Revised 09th July 2014
Accepted 10th July 2014
Online 30th July 2014