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Original Research Article

Thermodynamics of the Solubility of Some Fluoroquinolones in n-Butanol

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Abstract

Purpose: This study was to investigate the solubility and determine the thermodynamic parameters of solubility of three fluoroquinolones in an organic solvent (n-butanol) so as to establish their correlation with their transfer (absorption and penetration of bacterial cell wall) processes.
Methods: The solubility of the three fluoroquinolones in n-butanol at different temperatures of 20 ^{o}C, 25 ^{o}C, 30 ^{o}C, 37 ^{o}C and 45 ^{o}C, was determined using UV-visible spectrophotometry at their appropriate wavelengths of maximum absorption.
Results: The results showed that the solubility of the fluoroquinolones in n-butanol increased with increasing temperature. Of the three fluoroquinolones studied, norfloxacin was the most soluble in n-butanol.
Conclusion: The solubilization process of these fluoroquinolones in n-butanol was non-spontaneous.

Keywords: Fluoroquinolones, thermodynamics, solubility, n-butanol

Indexing: Index Copernicus, African Index Medicus

Introduction

In recent years, there has been a remarkable progress in the development of the derivatives of nalidixic acid and the most important development is the introduction of a fluorine substituent at the C-6 position, which led to the production of the class of quinolones referred to as fluoroquinolones which have greater activity against many difficult-to-treat bacteria [1].

It was the synthesis of these fluorinated quinolones known as fluoroquinolones that really opened up the field of quinolone antibacterial chemotherapy. These fluorinated quinolones are characterized by very low minimum inhibitory concentrations (MIC) for Enterobacteriaceae and a moderate activity against *Pseudomonas aeruginosa* and Staphylococcal species [2,3].

The differences in the activity of the quinolones are as a result of the differences in substituents [4] which may be responsible for differences in absorption and tissue penetration which may potentially be predicted by their physicochemical properties [5]. Studies on solubility in organic medium and the thermodynamics of the solubility are very important to understanding the transportation of the drugs across biologic membranes, whether bacterial or gastrointestinal membranes. This is because the bioavailability of a drug, minimum inhibitory concentration (MIC) and hence its antimicrobial activity are dependent on the entry of the drug molecule into the bacterial cell and its interaction with its target within the cell. Therefore, for the quinolone drug to be active, it has to be present in appropriate concentration at the site of action and must necessarily be absorbed through various membranes [6-8].

Lipid solubility (lipophilicity) is one of the most important determinants of the pharmacokinetic characteristics of a drug since it relates to the absorption of the drug as well as the distribution of the drug to its target site. It is now generally recognized that the more lipophilic a compound, the better its ability to cross the lipid membrane barriers and hence increased absorption [8,9].

Drugs, therefore, must pass through the lipoidal film and in doing so, they must partition from an aqueous environment on the gastrointestinal lumen into the lipoidal membrane barrier and through this predominantly lipoidal environment in the membrane, and then from the membrane barrier into the aqueous environment of the blood or lymphatics that is on the other side of the membrane [9,10]

So if the drug does not have a propensity for the lipoidal barrier, it will tend to remain in solution in the gastrointestinal tract. It is therefore necessary that the drug have some affinity for the lipoidal gastrointestinal membrane since lipid solubility is an important physicochemical property that governs the transfer through the biological membrane barriers [10, 11].

Attempts have been made to simulate bio-membranes using simple solvent systems, and the organic solvent of choice in most cases is n-octanol. The octanol-water system has been found to be a useful reference solvent for *in vitro* studies since it closely simulates the aqueous-lipid barriers found in the body, [12 − 14]. However, Davies et al. have argued that less polar and inert solvents such as cyclohexane and some other alcohols would be more suitable from a thermodynamic standpoint [15]. Infact, solvents like cyclohexane have been found to yield good correlations with the partitioning of solutes obtained in model membranes compared to non-polar solvents [15,16]

The application of the principles of thermodynamics has long been recognized as the most fundamental approach to the study of physical and chemical changes such as solubility and partitioning. Biological processes are essentially physical and chemical by nature and are therefore controlled by the exchange of energy, so that thermodynamic concepts are also applicable to biological systems [15].

The spontaineity of chemical reactions depends on the relative size of the enthalpy and entropy values. Free energy is a state function that relates the first and the second laws of thermodynamics. The energy value which is given by the change in Gibbs free energy (ΔG) represents the combined contribution of the change in enthalpy (ΔH) and change in entropy (ΔS) values for a chemical reaction; therefore, change in free energy (ΔG) is the ultimate or absolute predicator of reaction spontaneity [17]. The purpose of this study was to evaluate the thermodynamics of the solubility of some fluoroquinolones in n-butanol.

Experimental

Materials

Ultra-violet/Visible spectrophotometer (UV/Vis Spectrometer, model T70, PG Instruments Ltd, United Kingdom), thermostated shaker bath (Gallenkamp, United Kingdom), water deioniser (Model 6C Houseman [Burnham] Ltd, United Kingdom), sensitive analytical balance (b15, Mettler, Toledo, Switzerland), pH meter (Model 3020, serial no. 4519, Jenway, United Kingdom) with a ThermoOrion combination glass electrode (Orion Research, Boston, MA).

The three fluoroquinolones used for this work were supplied by reputable Pharmaceutical Companies in Nigeria. Norfloxacin and ciprofloxacin were obtained from Sam Pharmaceuticals (Ilorin, Nigeria) and ofloxacin (manufactured by Hoechst, Germany) was obtained from Nigeria-German Company (Lagos, Nigeria). Analytical grade of n-butanol (Sigma-Aldrich, Germany) was obtained from local supplier.

Methods

Calibration Plot for the Fluoroquinolones in n-Butanol

Stock solutions of ciprofloxacin (5 mg/100ml), ofloxacin (10 mg/100ml) and norfloxacin (10 mg/100ml) were prepared in n-butanol as an organic medium. The solutions were wrapped in aluminium foil and stored in amber coloured bottles to prevent or minimize photodegradation. Standard solutions (25 ml each) of the fluoroquinolones in n-butanol were then prepared using aliquots of 0.0, 0.5, 1.0, 1.5, 2.0 and 2.5 ml of the stock solution and the absorbance of each of the final solution was measured at 260 and 300nm using the spectrophotometer. Beer-Lambert's (calibration) plots for the three fluoroquinolones were then prepared by plotting absorbance values against the concentrations of fluoroquinolone.

Determination of the Solubility of Fluoroquinolone in n-Butanol

Known weights (20 mg each) of finely divided pure fluoroquinolone powder were placed in dried and clean volumetric flasks and 5 ml of n-butanol was added to simulate lipoid organic membrane. The solutions were protected from light by wrapping the flasks in aluminium foil and agitated for 5 h in a temperature-regulated water bath set at 20^o, 25^o, 30^o, $37^o$and 45^oC, ($\pm 0.1^o$C) respectively. After equilibrium was achieved, a 1 ml clear solution was removed from the saturated solution in the flask and serially diluted with n-butanol and the absorbances of the final solutions were measured using the spectrophotometer at wavelengths of maximum absorption already determined with the pure fluoroquinolones above. From the absorbance values, the solubilities of the fluoroquinolones in n-butanol were calculated after interpolation of corresponding concentration from already prepared calibration plots. Based on the solubility at different temperatures, van't Hoff plot of ln S versus 1/T (reciprocal of temperature) was prepared and the thermodynamic parameters of the solubility of the fluoroquinolones in n-butanol were calculated.

Results and Discussion

In the organic medium used, the solubilities of these fluoroquinolones were lower than they were in the aqueous buffer at the thermodynamic temperature of 25 ^{o}C. In n-butanol, the solubilities are as follows: 77.50 µg/ml (2.01 x 10^{-4} M) for ciprofloxacin, 162.50 µg/ml (4.50 x 10^{-4} M) for ofloxacin and 225.00 µg/ml (7.05 x 10^{-4} M) for norfloxacin. Of the three fluoroquinolones, norfloxacin was the most soluble in n-butanol.As the temperature icreased, the solubility of the compounds slightly increased.

The van't Hoff plots (Figure 1) for the solubilities was linear with negative slopes and correlation coefficients (r^2) greater than 0.99 and hence the van't Hoff method was useful for the respective thermodynamic analyses [18-20].

From the van't Hoff plots, the thermodynamic functions (standard changes in free energy, enthalpy and entropy) of the solubilities of the compounds are summarized in Table 1. The analysis made by considering the sign and magnitude of the respective thermodynamic functions has been traditionally relevant in explaining the basis of reactions at molecular level.

The standard free energy change of solubilization *(ΔG°_{s}) in n-butanol at 25 ^{o}C also gave positive values in all the cases; +21.08 KJ/mol for ciprofloxacin, +19.09 KJ/mol for ofloxacin and +18.00 KJ/mol for norfloxacin. The smaller the free energy (ΔG°_{s}) values, the greater the solubility of a compound since it will take lesser energy to break the crystal lattice structure.

Generally, the standard free energy change of solubilization (ΔG°_{s}) for each of the three fluoroquinolones was higher in n-butanol than in the buffered aqueous medium so that more energy or work is needed for the fluoroquinolones to be soluble in n-butanol compared to the aqueous medium [18]. From the results, the solubilization of the three fluoroquinolones in n-butanol also increased with increasing temperature and the spontaneity of the solubilization was dependent on temperature as well as the relative size of the standard change in enthalpies (ΔH°_{s}) and the standard change in entropies (ΔS°_{s}). The standard changes in enthalpy of solubilization (ΔH°_{s}) of the fluoroquinolones are as follows: +17.82 KJ/mol for ciprofloxacin, +11.78 KJ/mol for ofloxacin and +9.48 KJ/mol for norfloxacin. The positive sign of the standard changes in enthalpy of solubilization in n-butanol for the three fluoroquinolones, showed that the process was endothermic.

The standard changes in entropy of solubilization (ΔS°_{s}) of the three fluoroquinolones gave negative values with a magnitude of –10.94 J/mol.K for ciprofloxacin and –24.55 J/mol.K for ofloxacin and –27.28 J/mol.K for norfloxacin. The entropy values reported as J/mol.K were low compared to the enthalpy values that are in KJ/mol. The negative sign

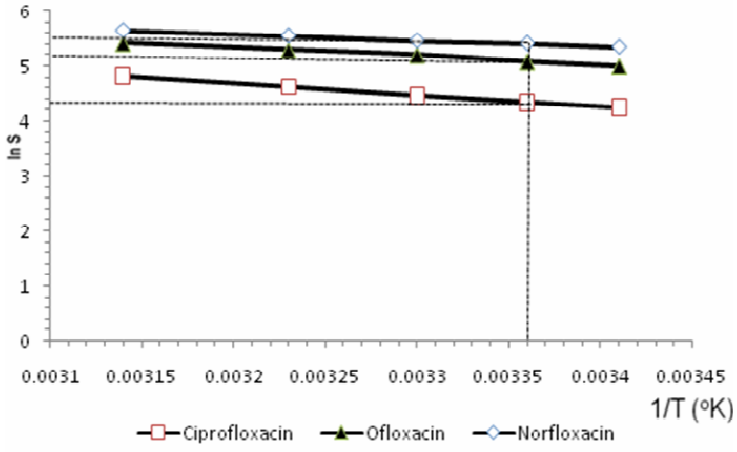

Figure 1: van't Hoff Plot of ln S versus 1/T for the solubility of fluoroquinolones in n-butanol

Table 1: Solubility and thermodynamic profiles fluoroquinolones in n-butanol at 25^{o}C

Fluoroquinolone	Slope of Plot (K^{-1})	ΔG°_{s} (KJ/mol)	ΔH°_{s} (KJ/mol)	ΔS°_{s} (J/mol.K)
Norfloxacin	-1139.80	+18.00	+9.48	-27.28
Ofloxacin	-1416.90	+19.09	+11.78	-24.55
Ciprofloxacin	-2143.40	+21.08	+17.82	-10.94

of the entropy values for the three fluoroquinolones showed that the solubilization was not entropy-driven because standard change in free energy increases as ΔS_s is negative. Thus, the $-T\Delta S^{\circ}_{s}$ term in the Gibbs free energy equation becomes positive and the standard change in free energy tends to be positive depending on the ΔH°_{s} contribution. The lesser the magnitude of the entropy values (i.e. more negative), the lesser free energy content and such processes are entropy-driven based on organizational changes in the medium.

Of the three fluoroquinolones studied, norfloxacin was most soluble in n-butanol. This was due to the fact that he much lower standard change in free energy, change in enthalpy and the change in entropy of solubility for norfloxacin in n-butanol (i.e. highest negative value) could be the explanation for this.

Conclusion

The thermodynamic parameters of solubilization of the fluoroquinolones in n-butanol, showed that the solubilization process of these fluoroquinolones was non-spontaneous. Energy barrier for their solubilization was overcome by increasing temperature and by work on the system through agitation which increased disorderliness and hence entropy. The solubilization of the three fluoroquinolones in n-butanol also increased with increasing temperature and the solubilization was dependent on temperature as well as the relative size of the standard change in enthalpies (ΔH°_{s}) and the standard change in entropies (ΔS°_{s}).

Conflict of Interest

No conflict of interest associated with this work.

Contribution to Authorship

We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by us.

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