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Research article

DETERMINATION OF SOLUBILITY AND THERMOPHYSICAL PROPERTIES OF TETRACYCLINE HYDROCHLORIDE AND CIPROFLOXACIN ANTIBIOTICS IN DIFFERENT SOLVENTS SYSTEM

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ABSTRACT: In this research article, we have described to establish a comparison between the solubility of the hydrochloride and non-hydrochlorideforms of ciprofloxacin and tetracycline in relevant solvents. For that purpose the solubility ofciprofloxacin and tetracycline were measured in water, methanol, propanol,and acetone, in the temperature range between 293.20 and 323.20 K for ciprofloxacin and between 288.20and 303.20 K for tetracycline. The solubility of the hydrochloride form in water is about 2 orders of magnitude higherthan those of the respective base forms. In acetone, we see the opposite effect. For methanol and propanolthe influence of the hydrochloride group of the antibiotic on the solubility in the alcohol is much smaller thanfor water and acetone. The experimental data was correlated with good results using two different activitycoefficient models, NRTL and UNIQUAC, with UNIQUAC giving better results, particularly for ciprofloxacin.The performance of COSMO-RS model to describe the studied systems was also evaluated.The dependence of these properties with temperature are shown. Theresults are interpreted in terms of solute-solvent interaction

Key Words: Tetracycline Hydrochloride, Ciprofloxacin, Solubility, Thermophysical Properties.

Abbreviations

γ_2: activity coefficient of the solute in solution, *τij:* temperature-dependent binary interaction parameter**,**F1: density of the solvent**,**F2 : apparent liquid density of the solute**,**FM : density of the solution**,**S : solid **,** L : liquid**,** fus: fusion, model =value calculated with the model, exp= experimental value. NRTL: non-random two-liquid model, UNIQUAC: Functional-group Activity Coefficients.

INTRODUCTION

The tetracycline consist of a polycyclic ring with differing side chains and is a broad-spectrum class of antibiotic against aerobes and anaerobes (Stoilova *et al., 2013,* Sanders *et al*., 1992, Brook *et al*., 2007). Members of this class inhibit protein synthesis by binding to the 30S ribosomal sub-unit thereby blocking the incoming aminoacyl-tRNA from attaching to the acceptor site on the mRNA-ribosome complex. The congener tetracycline is a product of Streptomyces aureofaciens fermentation.Tetracycline is bacteriostatic and their effects are reduced by dilution and by chelation with divalent cations. The tetracycline is broad-spectrum antibiotic, but resistance to one congener confers resistance to all congeners (Testa *et al*., 1993).

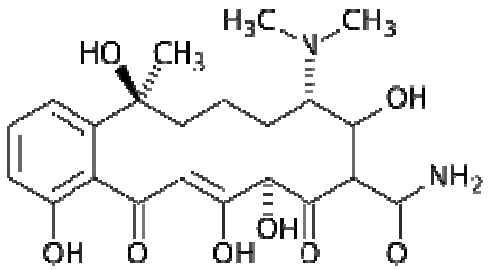

Figure 1A: Structure of Tetracycline

CIPRO (ciprofloxacin hydrochloride) Tablets and CIPRO (ciprofloxacin) Oral Suspension is synthetic broad spectrum antimicrobial agent for oral administration. Ciprofloxacin hydrochloride, USP, a fluoroquinolone, is the mono-hydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. It is a faintly yellowish to light yellow crystalline substance with a molecular weight of 385.8. Its empirical formula is C17H18FN3O3•HCl•H2O and its chemical structure is as follows. These drugs will have a brightfuture owing to their extremely potent antibacterial activity, rapidbactericidal effects, and a better safety profile than otherantimicrobial agents, including the older quinolones, such asciprofloxacin, oxofloxacin, norfloxacin, lomefloxacin, and ciprofloxacin (Rubinstein *et al*.,2000, Bernhard *et al.,* 1998,Goldstein *et al*.,1998) . Since their behaviour in vivo greatly dependson their degree of ionization, lypophylicity, and conformationalcharacteristics, the related thermo-physical properties have beenplaying an important role in the rational drug design during thelast nearly 3 decades (Ji *et al*., 2013).

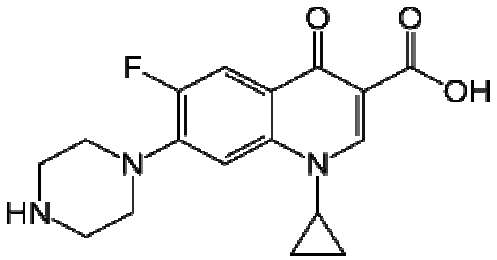

Figure 1B: Structure of ciprofloxacin hydrochloride

In particular, the solubility of active principles in selectedsolvents is of overwhelming importance for the identificationof drug delivery pathways in order to develop more efficient active pharmaceutical ingredients (APIs) (Nielsen *et al., 2013,* Breda *et al.,2008*). This information isextremely valuable to define profiles of administration, distribution,metabolism, excretion, and toxicity of drugs. Although thesolubility of drugs plays a decisive role in the process of drugdiscovery, experimental data at the desired conditions is still scarce and most of the time unavailable. The development ofa reliable model to predict the solubility of drugs would beextremely useful. The fact that these molecules are typicallycomposed of several interlinked aromatic cores and multiple substituent containing heteroatoms N, P, O, S, and F or Cl,liable to a variety of specific interactions with polar solvents,e.g., protonation, hydrogen bonding, specific solvation, and conformally flexible, makes this task very complicated. Classicalthermodynamic models, such as activity coefficient models likeNRTL, UNIQUAC, or UNIFAC, are frequently used to model solid-liquid equilibria (SLE), including the solubility ofAPIs in solvents. Thus, the choice is to use classicalthermodynamic models to correlate the available solubility datain order better understanding the behaviour at the molecular level. In this the present research program (Breda *et al.,2008*). The antibiotics showed to have the same solubility order, that is, they are more soluble in water than in methanol, more soluble in methanol than in 2-propanol and acetone. The solubility in water is about 3 orders of magnitude higher than in acetone. The modelling of the experimental solid-liquid equilibrium data, using NRTL and UNIQUAC, proves that these models can correlate satisfactorily the solubility of the studied antibiotics (Poplewska *et al.,* 2008, Abrams *et al*.,1997).

MATERIALS

Tetracycline and Ciprofloxacin were purchased from Biogenix, India (98% and >99.8%) purity. Methanol absolute and acetone for GC with purity99%, propanol ACS reagent for UVspectroscopy with purity of 99.8%, and ethylacetate 99.8% is from Laboratory-Scan. All of them areanalytical reagents and were used without further purification.Deionized and double-distilled water was used.

METHOD

The solubility of ciprofloxacinin water, methanol, propanol, and acetone at 293.20, 303.15,313. 20, and 323.20K and tetracycline in the same solvents at288.20, 293.20, and 303.20 K was measured. The solubility oftetracycline was only studied at temperatures up to 310.20 K, since it decomposes at higher temperatures. Sealed Erlenmeyer flasks containing an excess of drug powderin the presence of a fixed volume of each of the pure solventswere equilibrated for 6 h at each temperature, in a temperaturecontrolledbath. For higher temperatures, 313.20 and 323.20 K,a thermostatic shaking bath wasused. For lower temperatures, 288.20 K, 293.20, and 303.20K, an air bath specifically built for this purpose, with temperaturecontrol of (0.2 K) was used. After the equilibrium was reached,the excess solid was allowed to settle down, the liquid phasewas sampled using a syringe with filter, and the composition was determined.

Characterization

UV spectroscopy:

UV spectroscopy (Shimadzu UV-160AUV-vis recording spectrophotometer) with quartz cells at thecorresponding wavelength of the maximum absorbance ofthe API in the solvent under study. It was confirmed that 6 h of contact is thenecessary time to achieve equilibrium. The antibiotics stabilitythroughout the duration of experiment was confirmed throughthe analysis of their UV spectra before and after the equilibriumexperiment.

Modelling

Activity Coefficient Models.

Solubility denotes thesolute concentration in a solution that is in thermodynamicequilibrium with the solute in the solid state. At phaseequilibrium, for any species *i*, the fugacities: *fi* must be thesame in all phases. The phase equilibrium equation for a solid-solute, designated by subscript 2, which partly dissolves ina liquid solvent, at a temperature *T* and a pressure *P*, can bewritten as

$$f_2^L(T,P,\{x^L\} = f_2^s(T,P,\{x^s\}) \qquad (1)$$

Where*x* denotes the mole fraction and the superscripts L and Sdenote the liquid and the solid phases, respectively. Assumingthat the solid phase consists only of pure solid ($x_2 = 1$), thefugacity of component 2 in the solid phase f_2^S is equal to thefugacity of the pure solid. The fugacity of component 2 inthe liquid phase f_2^L can be calculated via the activity coefficient. After introduction into eq(1) we get

$$x_2\gamma_{2\ (T,P,x_2)}f_2^L(T,P) = f_2^s(T,P) \quad (2)$$

Whereγ_2 is the activity coefficient of the solute in the liquidphase. Further assumptions lead to the following simplifiedequation that was used to calculate the mole fraction of the solute in the solvent:

$$\ln x_2 = -\ln\gamma_2 - \frac{\Delta_{fus}H(T_{mp})}{RT}\left[1 - \frac{T}{T_{mp}}\right] \qquad (3)$$

T_{mp} is the melting point temperature; $\Delta_{fus}H$is the enthalpyof fusion. A more detailed derivation of eq (3) can be found inthe literature (Abrams *et al*.,1997, Gracin *et al*., 2002Sandler *et al*., 1999, Prausnitz *et al*., 1999)

Two activity coefficient models were used to calculate theactivity coefficients of the solute: NRTL and UNIQUAC. The equations were used as described previously. For the interaction parameters, τij, for NRTL (Feleilnik *et al*., 2007) as well as for UNIQUAC (Varanda et al., 2006, Renon *et al*; 1968) the following temperature dependence was used:

$$T_{ij} = a_{ij} + \frac{b_{ij}}{T} \quad (4)$$

$a_{ij}$and $b_{ij}$are adjustable parameters. Unlike the modelling of the hydrochloride forms, where for one system (water +tetracycline · HCl) both a_{ij} and b_{ij} had to be used to give a goodrepresentation of the experimental data, for all systems investigatedin this work, either the use of a_{ij}or b_{ij} values is sufficient. For some binary systems, especially those where the experimentaldata cover just a small temperature range, the use of the temperature-independent parameters a_{12} and a_{21} are sufficient. We used parameters b_{ij} for all systems investigated and set parameters a_{ij}equal to zero. For alarge number of binary systems, nonrandomness factor R_{12} ofthe NRTL model varies between 0.20 and 0.47.13 We set $R_{12}$to 0.25 for all calculations, being the standard value for theVTPLAN [18] process simulator of Bayer. The values for thestructural parameters *r* and *q* of the UNIQUAC model are listedin Table 1.

For the solvents, they have been taken from the Dortmund Data Bank. (Abrams *et al.,*1975) For the antibiotics, the Bondi group contribution method was used to calculate them.

Table .1 : Thermo physical Properties of the Antibiotics and Solvents used in the Modelling

Compound	MW (g. mol^{-1})	T_{mp}K	$\Delta_{fus}H$ j..mol^{-1}	□ Kg.m^{-3}	UNIQUAC	
					f	q
Tetracycline base	444.4	445.65	251830	1182.14	17.627	14.70
Ciprofloxacin base	331.35	541	30570	1508.10	11.412	8.356
water	18.02	273.15	18492		0.9200	1.400
Methanol	32.04	175	3.1773 kJ/mol		2.1052	1.971
propanol	60.10	184.65	1498.0		2.7791	2.508
acetone	58.08	178.45	1711.6		2.5735	2.335

In order to correlate the experimental data using eq(3), pure component solute properties such as T_{mp} and $\Delta_{fus}H$are needed. The value of the melting point temperature fortetracycline was taken from the literature (Poling *et al*., 2001). The experimentaldetermination of the melting temperature of ciprofloxacin ischallenging since it decomposes during melting. The MerckIndex gives a decomposition temperature of 528-530 K.The influence of the heatingrate on the melting behaviour of fluoro-quinolones in a glass-capillary apparatus. At a heating rate of 3 K/min decompositionand melting of ciprofloxacin was observed between 530and 542 K, whereas at a heating rate of 5 K/min it waspossible to determine a clear melting interval (538.5-544.6K). As an input parameter for the solubility modelling we used (T_{mp} 541 K) for ciprofloxacin. As compared to themelting point of ciprofloxacin hydrochloride (592.15 K) the value of the base form is 51 K (8.6%) lower. This is the expected behaviour, since in almost all casesthe hydrochloride forms of organic compounds show present behaviour of salts. The melting points of organic salts arehigher than those of their base form since they also interactby ionic electrostatic forces which are more energetic thanthose presented among non-ionic compounds, such as hydrogen bonding and vander-Waals interactions (Neil *et al.,*2006). For tetracycline, the melting point of the base form is 36.5 K (7.6%) higherthan that of the hydrochloric form. The values for the meltingpoints of all substances investigated are given in Table 1. No experimental enthalpies of fusion data were available forany of the antibiotics. These values were calculated using thefollowing relationship:

$$\Delta_{fus}H = T_{mp}\Delta_{fus}S \quad (5)$$

While$\Delta_{fus}S$ was taken to be constant and equal to 56.51 Jmol-1 K^{-1} as suggested that the entropy of fusion of many drugsand rigid molecules of intermediate size can be estimated by using this value. Thecalculated melting enthalpies for the antibiotics are reportedin Table 1, as well as the pure solvent properties taken fromthe DIPPR data-base.

To calculate mole fractions from the solubility data, thedensity of the solution FM needs to be known. Densities ofantibiotic solutions were measured using the gravimetric method. The data points could be regressed within experimental accuracyusing the following equation:

$$\rho_M = \rho_1\left(1 - \frac{s}{\rho_2} + \frac{s}{\rho_1}\right) \quad (6)$$

For the temperature-dependent solvent densities F1, data weretaken from the DIPPR data-base. The apparent liquid densityof the solute (antibiotic) F_2 was used as a regression parameter.

F_2 was assumed to be independent of temperature within theinvestigated temperature range, which lies well below themelting temperature of the antibiotics. Values for F_2 are given in Table 1.

The NRTL and UNIQUAC model parameters were obtainedby fitting the experimental solubility data. The objectivefunction, *F*, which was used in order to adjust the modelparameters, is of the form.

$$F = \left[\frac{1}{NP}\sum_{i=1}^{NP}(D_i - 1)^2\right]^{1/2} \quad (7)$$

Where*i* denotes a data point, NP is the number of data points,and

$$D_i = \left(x_{exp}\gamma_{model}\right)/exp\left[-\frac{\Delta_{fus}H(T_{mp})}{RT}\left(1 - T/T_{mp}\right)\right] \quad (8)$$

RESULTS AND DISCUSSION

Tables 2 and 3 list the experimental results for the solubility of the two studied antibiotics in the above-mentioned solvents. The solubility, *S* (milligrams of antibiotic per millilitre of solution), is an average of at least three agreeing independent experiments. The corresponding standard deviation, sd, for each mean value is also reported (*Dorofeev et al*.,2004, Alizadeh *et al*., 2012, Ghasemi *et al*., 2011).

Table 2 : Mole Fraction, *x*, Solubility, *S*, in Milligrams of Antibiotic per Millilitre of Solution, and Standard Deviation, sd, of Tetracycline in Different Solvents at Temperatures between 288.20 and 303.20 K

Solvent	T=288.20 K			T=293.20 K			T=303.20 K		
	$x/10^{-3}$	s	sd	$x/10^{-3}$	S	sd	$x/10^{-3}$	s	sd
water	0.0081	0.202	0.008	0.0125	0.312	0.025	0.0165	0.420	0.03
propanol	0.397	2.31	0.26	0.561	3.24	0.04	0.737	4.23	0.35
acetone	4.98	30.0	0.8	5.21	31.0	1.7	7.78	45.3	0.7
Methanol	6.12	45.6	0.09	7.33	54.0	3.4	11.4	82.44	0.31

Table 3 : Mole Fraction, *x*, Solubility, *S*, in Milligrams of Antibiotic per Millilitre of Solution, and Standard Deviation, sd, of Ciprofloxacin in Different Solvents at Temperatures between 293.20 and 323.20 K

Solvent	T=293.20 K			T=303.20 K			T=313.20 K		
	$x/10^{-5}$	s	sd	$x/10^{-5}$	S	sd	$x/10^{-5}$	s	sd
water	0.364	0.066	0.004	0.436	0.081	0.011	0.648	0.120	0.010
propanol	1.267	0.053	0.006	2.145	0.093	0.014	3.280	0.138	0.006
acetone	2.466	0.106	0.007	3.677	0.165	0.001	7.576	0.332	0.001
Methanol	0.808	0.045	0.0023	1.405	0.078	0.012	2.011	0.111	0.011

When the solubility results obtained for the two antibiotics are analyzed, it is possible to see that the solubility of a compound is determined by both the properties of the solvent and of the pure solid in equilibrium with the solvent. Ciprofloxacin shows a poor solubility in water and in the two studied alcohols, and the solubility in acetone is usually 1 order of magnitude larger than in the other solvents. As for tetracycline, the solubility order is water <propanol <methanol~ acetone. The solubility in methanol and acetone is similar and 2 orders of magnitude larger than in water. Surprisingly, the solubility in propanol is intermediate between water and the other solvents, indicating that the structure of the alcohol plays an important role in the solvation of the antibiotics. These behaviours are quite different from the ones found for the respective hydrochloride forms where the solubility in water is about 3 orders of magnitude higher than in acetone, for a given temperature. A comparison between the solubility of these two antibiotics is presented in Figures 2 and 3, and it can be observed that, for all the solvents, the solubility of tetracycline is larger than those of ciprofloxacin. This fact indicates that this API might possibly have a lower bio-availability due to its poor solubility in biological fluids, which are basically aqueous solutions. Also, since ciprofloxacin is a totally man-made antibiotic its solubility in common solvents is very important in synthesis of improved structure-activity drugs and also in the purification steps.

The influence of the hydrochloride group on the solubility of tetracycline and ciprofloxacin in different solvents can be seen when the experimental results are compared with data of tetracycline · HCl and ciprofloxacin · HCl from our previous study. Figure 4 compares the results for tetracycline and tetracycline · HCl both in water and in acetone. The solubility of the hydrochloride form in water is about 2 orders of magnitude higher than that of the base form. This is probably due to the presence of the hydrochloride group, which in water leads to the formation of ionic species and the protonation of the amine group in both antibiotics which interact with water by ion-dipole thus increasing the aqueous solubility. In acetone we see the reverse effect; the solubility of the base form is 2 orders of magnitude higher than that of the hydrochloride form. For the two alcohols investigated, the solubility of tetracycline base is 1 order of magnitude higher than that of tetracycline · HCl (Breda *et al*., 2008, Nielsen*et al.,*2013). The solubility of ciprofloxacin hydrochloride in both alcohols is similar to the solubility of ciprofloxacin base. However, its solubility in water is more than 2 orders of magnitude higher than that of the base form (Figure 5). The solubility of ciprofloxacin base in acetone is about 1 order of magnitude higher as compared to the hydrochloride form (below detection limit of 0.01 mg/mL) and thus possible to be measured. In the present investigation,the experimental data with both models are very good. Comparison of UNIQUAC correlations with theexperimental data are shown graphically in Figures 2 and 3. The solubility of tetracycline cover several orders of magnitude,e.g., at 283.20K from 0.2 (water) to 45.7 (methanol) mg/ml. All curves were calculated with two adjustable parameters for each binary system.

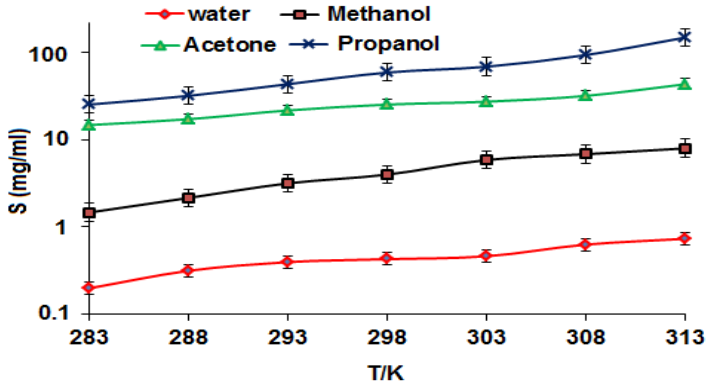

Figure 2.Experimental solubility data for tetracycline base in water, methanol, acetone, and propanol. The lines represent modelling using UNIQUAC.

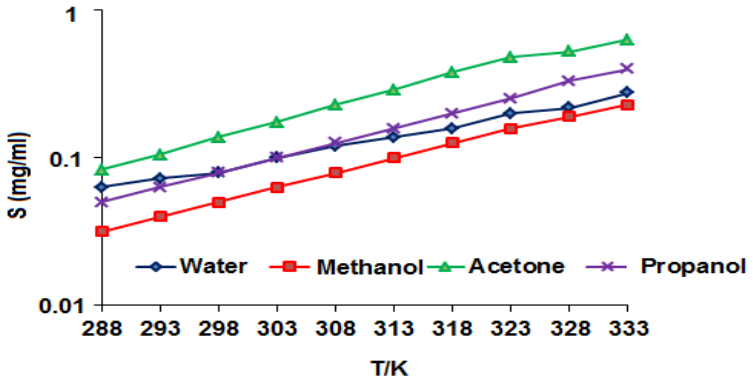

Figure 3.Experimental solubility data for ciprofloxacin base in water, methanol , acetone , and propanol . The lines represent modelling using UNIQUAC

Table 4. Optimized Parameters for the UNIQUAC and NRTL Models and Respective Average Absolute Deviations (AAD) and Relative Absolute Errors (RAE) for the Solubility of Tetracycline in Several Solvents

Solvent	NRTL Model				UNIQUAC Model			
	b_{12}	b_{21}	AAD mg/ml	RAE %	b_{12}	b_{21}	AAD mg/ml	RAE %
water	1992.61	2412.71	0.027	8.4	26.35	-224.16	0.022	7.83
Methanol	612.48	-175.35	1.114	1.7	72.14	-317.61	0.765	1.46
propanol	882.44	2461.63	0.195	6.0	**77.21**	-417.82	0.181	5.84
acetone	163.28	2320.04	1.336	**4.6**	120.87	-432.24	1.494	4.74

Table 5. Optimized Parameters for the UNIQUAC and NRTL Models and Respective AADs and RAEs for the Solubility of Ciprofloxacin in Several Solvents

Solvent	NRTL Model				UNIQUAC Model			
	b_{12}	b_{21}	AAD mg/ml	RAE %	b_{12}	b_{21}	AAD mg/ml	RAE %
water	1766.42	2443.31	0.0374	30.2	-404.18	235.58	0.0034	4.2
Methanol	1464.01	2457.27	0.0063	6.2	-657.57	252.67	0.0032	3.5
propanol	1340.12	2475.61	0.0136	9.3	-648.77	265.37	0.0078	6.2
acetone	1447.59	-8.895	0.0163	6.0	-260.06	49.98	0.0105	5.3

The optimized parameters for the two models used to describethe solubility of tetracycline and ciprofloxacin along with theaverage absolute deviation (AAD) and the relative absolute error(RAE) of the models are presented in Tables 4 and 5,respectively. Overall, the difference between the modelling results of UNIQUAC and NRTL is small. For the ciprofloxacinsystems, UNIQUAC with two parameters is better than NRTLwith two parameters (R set to 0.25) to describe the temperaturedependence of the solubility, particularly for water. For thetetracycline systems, the difference between the modelling resultsof UNIQUAC and NRTL is small.

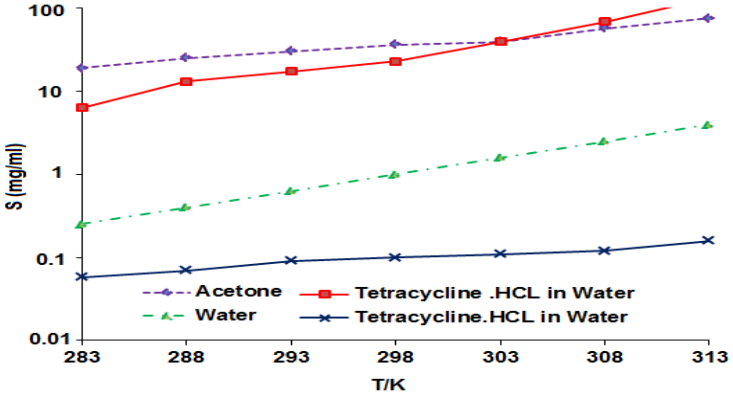

Figure 4.Comparison of the solubility of the base form and hydrochloride form: tetracycline base in water and in acetone, tetracycline · HCl in water and in acetone. Lines represent modelling using UNIQUAC: solid lines are the hydrochloride form, broken lines are the base form.

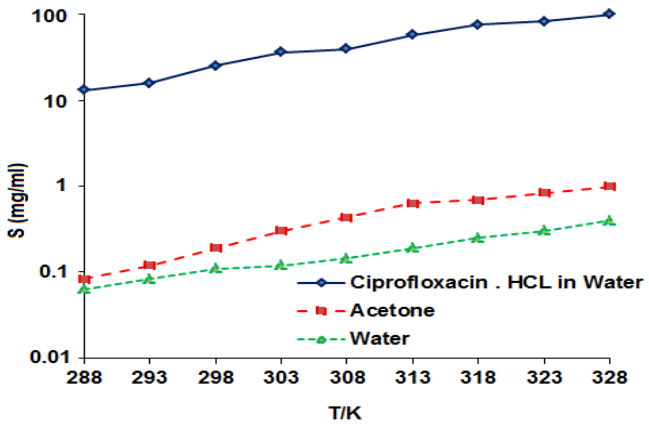

Figure 5.Comparison of the solubility of the base form and hydrochloride form: ciprofloxacin base in water and in acetone, ciprofloxacin · HCl in water and in acetone below the detection limit of 0.01 mg/ml. Lines represent modelling using UNIQUAC: solid lines are the hydrochloride form, broken lines are the base form.

From Figures 4 and 5 it can be concluded that the effect ofthe hydrochloride group on the solubility in different solventscan be well correlated with an activity coefficient model, like UNIQUAC.

The modelling results should be, of course, viewed taking intoaccount that the melting temperature of ciprofloxacin base couldnot be precisely determined, due to thermal decomposition, as well as predicted $\Delta_{fus}H$ values were used for both antibiotics. Furthermore, in the derivation of eq(3) the difference of the isobaric heat capacity of the solid and the liquid state, ΔC_p, was assumed to be zero for both antibiotics due to lack ofexperimental data, although the temperatures considered werefar away from the melting point temperatures of the antibiotics. On the other hand a sensitivity analysis showed that most of the uncertainties are completely compensated by the fitting ofthe binary interaction parameters b_{ij}. This shall be illustratedwith an example. When the melting point of ciprofloxacin base is estimated 5% higher while $\Delta_{fus}H$ and the NRTL parameters are kept constant, then the calculated solubility in acetone isreduced by 31%. When $\Delta_{fus}H$is calculated with eq 5 using the5% higher value for T_{mp}, then the solubility is even 44% lower than the experimental values. When, in a third step, the NRTLparameters $b12$ and $b21$ are optimized, then the representationof the experimental results is almost identical with the calculationusing the original values for Tmp, $\Delta_{fus}H$, b_{12}, and b_{21}. Thoughthese findings are true for the systems investigated in this work,they cannot be generalized, particularly not when a largeconcentration range is covered in the modelling. For example,in the moxifloxacin · HCl + water system, a value of $\Delta_{fus}H$thatis 10% lower than the value calculated with eq(5) leads to theoccurrence of a maximum in the composition dependence ofthe activity coefficient.

COSMO-RS.

The COSMO-RS method is a combinationof the quantum chemical dielectric continuum solvation modelCOSMO with a statistical thermodynamics treatment for realisticsolvation simulations. It has been found to be extremely helpfulin predicting liquid-liquid and vapor-liquid equilibria ofmixtures of a wide variety of substances from organic solventsto ionic liquids. It has also been used to predict, at least inqualitative way, the aqueous solubility of complex moleculessuch as drugs and pesticides.

However, its application to pharmaceutical compounds ismost of the times hindered by the large number of micro-speciespresent in solution that most of the drugs present. In thetetracycline case it is well documented in the literature that inwater there are a variety of zwitter-ionic hydrated forms withdifferent structures, whereas in organic solutions differenttautomers and conformers were found according to thesolvent. These facts made the use of COSMO-RS for thedetermination of tetracycline solubility virtually impossible (Klamt*et al*.,2002, Stezowski*et al*., 1976, Pavelka*et al*., 2007). On the other hand, ciprofloxacin is an amphoteric API, withfour possible micro-species present in aqueous solution, dependingon the pH. In the present case the pH was monitored duringthe solubilisation procedure, and its value was found to be equalto 7.5. According to the microspeciation diagram, at this pHmore than 90% of the ciprofloxacin is present in its zwitter-ionicform. In organic solvents ciprofloxacin is neutral. Thus,when using COSMO-RS two micro-species of this drug wereconsidered: the zwitter-ionic for the water and the neutral forthe organic solvents solubility calculations. The pure predictive resultsobtained by COSMO-RS for the ciprofloxacin were onlyaccurate in relative terms, and the problem was addressed tothe evaluation of $\Delta fus G$.In fact, the $\Delta fus G$calculated using QSAR methodspresented a very strong temperature dependence, while usingand adjusted $\Delta fus G$to each solubility data point indicated thatthis parameter was almost temperature-independent but surprisinglyquite different from solvent to solvent. If $\Delta fus G$is takenas an average value of the all obtained values ($\Delta fus G$)=5.4kcal/mol the deviations range between 2 and 3 orders ofmagnitude.

Therefore, the procedure adopted in this work is totreat this parameter as an adjustable parameter to each system, including water, and to fix it equal to the value obtained for theexperimental solubility data at 313.20K. The results of theCOSMO-RS predictions for the other temperatures for eachsystem are depicted in Figure 6. As can be seen, the model isable not only to capture the solubility sequence for the organiccompounds but also provides a fairly good description of theciprofloxacin solubility in quantitative terms. As for the solubilityof ciprofloxacin in water, although the results may not seemvery encouraging since COSMO-RS does not predict the correct dependence with temperature, the deviations are smaller than 1order of magnitude.

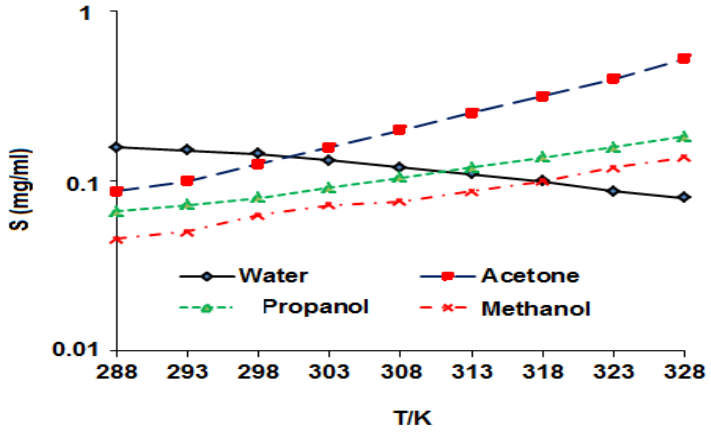

Figure 6.Solubility data for ciprofloxacin base in water ,methanol, acetone , and propanol using COSMO-RS

CONCLUSION

The present study shows the experimental data of solubility were obtained fortetracycline and ciprofloxacin in several solvents: water, methanol, propanol, and acetone. Again, the spectrophoto-metric method has proved to be an adequate tool for the determination of thesolubility of those antibiotics. The solubility of the two studiedantibiotics is dependent not only on the solute's properties butalso on the solute-solvent interactions. Ciprofloxacin shows apoor solubility in water and in the two studied alcohols, andthe solubility in acetone is usually 1 order of magnitude largerthan that in the other solvents. As for tetracycline, the solubilityorder is water <propanol <methanol ~ acetone. Surprisingly, the solubility in propanol is intermediate between water andthe other solvents, indicating that the structure of the alcoholplays an important role in the solvation of the antibiotic. The solubility of the hydrochloride forms of the two antibiotics inwater are about 2 orders of magnitude higher than those of theirbase forms. In acetone we see the reverse effect; the solubility of the base forms is much higher than those of the hydrochloride forms.

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