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APPLIED CHEMISTRY

Solubility of Antibiotics in Different Solvents. Part II. Non-Hydrochloride Forms of Tetracycline and Ciprofloxacin

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The aim of this work is to establish a comparison between the solubility of the hydrochloride and non-hydrochloride forms of ciprofloxacin and tetracycline in relevant solvents. For that purpose the solubilities of the non-hydrochloride forms of ciprofloxacin and tetracycline were measured in water, ethanol, 2-propanol, and acetone, in the temperature range between 293.15 and 323.15 K for ciprofloxacin and between 288.15 and 303.15 K for tetracycline. The obtained results were compared with those of part I of this study, published previously, where the solubilities of the respective hydrochloride forms of the antibiotics in the same solvents were investigated. The solubility of the hydrochloride forms in water is about 2 orders of magnitude higher than those of the respective base forms. In acetone, we see the opposite effect. For ethanol and 2-propanol the influence of the hydrochloride group of the antibiotic on the solubility in the alcohol is much smaller than for water and acetone. The experimental data was correlated with good results using two different activity coefficient 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.

1. Introduction

Quinolones are the first entirely man-made antibiotics and are a landmark discovery in the treatment of bacterial infections. The fourth generation of fluoroquinolones (levofloxacin, sparfloxacin, trovafloxacin, grepafloxacin, and moxifloxacin) are strongly effective antibacterial agents against a broader spectrum of Gram-positive and Gram-negative bacteria, which have become a major class of synthetic antibacterial agents under extensive clinical development. These drugs will have a bright future owing to their extremely potent antibacterial activity, rapid bactericidal effects, and a better safety profile than other antimicrobial agents, including the older quinolones, such as ciprofloxacin, oxofloxacin, norfloxacin, lomefloxacin, and enofloxacin.[12,13] Since their behavior in vivo greatly depends on their degree of ionization, lypophylicity, and conformational characteristics, the related thermophysical properties have been playing an important role in the rational drug design during the last nearly 3 decades.[1,2]

In particular, the solubility of active principles in selected solvents is of overwhelming importance for the identification of drug delivery pathways in order to develop more efficient active pharmaceutical ingredients (APIs). This information is extremely valuable to define profiles of administration, distribution, metabolism, excretion, and toxicity of drugs. Although the solubility of drugs plays a decisive role in the process of drug discovery, experimental data at the desired conditions is still scarce and most of the times unavailable. The development of a reliable model to predict the solubility of drugs would be extremely useful. The fact that these molecules are typically composed of several interlinked aromatic cores and multiple substituents 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. Classical thermodynamic models, such as activity coefficient models like NRTL, UNIQUAC, or UNIFAC, are frequently used to model solid–liquid equilibria (SLE),[3–9] including the solubility of APIs in solvents.[8–10] Thus, the choice is to use classical thermodynamic models to correlate the available solubility data in order better understanding the behavior at the molecular level.

This work is part of an ongoing project which aims at providing a better understanding of the solubility mechanisms of APIs in several solvents, by presenting original data on solubilities of antibiotics, ciprofloxacin and tetracycline (Figure 1), in selected solvents and also by testing the description provided by classical models. Moxifloxacin was not used in this study since the non-hydrochloride form is not a byproduct of the synthesis of moxifloxacin hydrochloride, and thus it is not available. In a previous work,[11] the solubilities of tetracycline hydrochloride, moxifloxacin hydrochloride, and ciprofloxacin hydrochloride in several solvents such as water, ethanol, 2-propanol, and acetone, in the temperature range were measured. All the studied antibiotics showed to have the same solubility order, that is, they are more soluble in water than in ethanol, more soluble in ethanol than in 2-propanol and acetone. The solubility in water is about 3 orders of magnitude higher than in acetone. The modeling of the experimental solid–liquid equilibrium data, using NRTL and UNIQUAC, proves that these models can correlate satisfactorily the solubility of the studied antibiotics.

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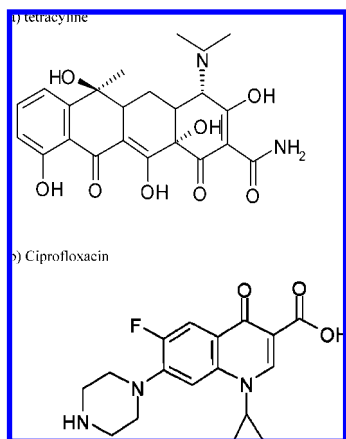
Figure 1. Structures of antibiotics molecules: (a) tetracycline base, (b) ciprofloxacin base.

2. Experimental Part

2.1. Materials. Tetracycline was purchased from Fluka (Sigma-Aldrich, 98% purity). Ciprofloxacin was generously provided by Bayer HealthCare AG with high purity (>99.8%). Ethanol absolute puriss. p.a. and acetone for GC with purity 99% are from Riedel de Hæn, 2-propanol ACS reagent for UV spectroscopy with purity of 99.8% is from Fluka, and ethyl acetate 99.8% is from Laboratory-Scan. All of them are analytical reagents and were used without further purification. Deionized and double-distilled water was used.

2.2. Experimental Procedure. The solubility of ciprofloxacin in water, ethanol, 2-propanol, and acetone at 293.15, 303.15, 313.15, and 323.15 K and tetracycline in the same solvents at 288.15, 293.15, and 303.15 K was measured. The solubility of tetracycline was only studied at temperatures up to 310.15 K, since it decomposes at higher temperatures.

Sealed Erlenmeyer flasks containing an excess of drug powder in the presence of a fixed volume of each of the pure solvents were equilibrated for 6 h at each temperature, in a temperature-controlled bath. For higher temperatures, 313.15 and 323.15 K, a thermostatic shaking bath (Julabo Shake Temp SW23) was used. For lower temperatures, 288.15 K, 293.15, and 303.15 K, an air bath specifically built for this purpose, with temperature control of ±0.2 K was used. After the equilibrium was reached, the excess solid was allowed to settle down, the liquid phase was sampled using a syringe with filter, and the composition was determined by UV spectroscopy (Shimadzu UV-160A UV−vis recording spectrophotometer) with quartz cells at the corresponding wavelength of the maximum of absorbance of the API in the solvent under study, according to Table 1 of our previous work.[11] It was confirmed that 6 h of contact is the necessary time to achieve equilibrium. The antibiotics stability throughout the duration of experiment was confirmed through the analysis of their UV spectra before and after the equilibrium experiment. Whenever necessary, the samples were diluted volumetrically with the respective solvent to obtain absorbances in the linear calibration range for each system. All the experimental results were an average of at least three agreeing independent measurements.

2.3. Experimental Results and Discussion. Tables 1 and 2 list the experimental results for the solubilities of the two studied antibiotics in the above-mentioned solvents. The solubility, S (milligrams of antibiotic per milliliter of solution), is an average of at least three agreeing independent experiments. The corresponding standard deviation, sd, for each mean value is also reported.

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 < 2-propanol < ethanol ∼ acetone. The solubility in ethanol and acetone is similar and 2 orders of magnitude larger than in water. Surprisingly, the solubility in 2-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 antibiotic. These behaviors 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 solubilities of these two antibiotics is presented in Figures 2 and 3, and it can be observed that, for all the solvents, the solubilities of tetracycline are larger than those of ciprofloxacin. This fact indicates that this API might possibly have a lower bioavailability 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.[11] 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.

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.

3. Modeling

3.1. Activity Coefficient Models. Solubility denotes the solute concentration in a solution that is in thermodynamic equilibrium with the solute in the solid state. At phase equilibrium, for any species i, the fugacities f_i must be the same in all phases. The phase equilibrium equation for a solid solute, designated by subscript 2, which partly dissolves in a liquid solvent, at a temperature T and a pressure P, can be written as

$$f_2^{L}(T, P, \{x^{L}\}) = f_2^{S}(T, P, \{x^{S}\}) \tag{1}$$

where x denotes the mole fraction and the superscripts L and S denote the liquid and the solid phases, respectively. Assuming that the solid phase consists only of pure solid ($x_2 = 1$), the

Table 1. Mole Fraction, x, Solubility, S, in Milligrams of Antibiotic per Milliliter of Solution, and Standard Deviation, sd, of Tetracycline in Different Solvents at Temperatures between 288.15 and 303.15 K

	$T = 288.15$ K			$T = 293.15$ K			$T = 303.15$ K		
solvent	$x/10^{-3}$	S	sd	$x/10^{-3}$	S	sd	$x/10^{-3}$	S	sd
water	0.0082	0.201	0.008	0.0126	0.311	0.024	0.0175	0.430	0.04
ethanol	6.13	45.7	0.09	7.32	54.0	3.3	11.5	82.5	0.3
2-propanol	0.398	2.32	0.26	0.562	3.25	0.03	0.739	4.22	0.36
acetone	4.99	30.0	0.8	5.20	31.0	1.8	7.79	45.4	0.8

Table 2. Mole Fraction, x, Solubility, S, in Milligrams of Antibiotic per Milliliter of Solution, and Standard Deviation, sd, of Ciprofloxacin in Different Solvents at Temperatures between 293.15 and 323.15 K

	$T = 293.15$ K			$T = 303.15$ K			$T = 313.15$ K			$T = 323.15$ K		
solvent	$x/10^{-5}$	S	sd	$x/10^{-5}$	S	sd	$x/10^{-5}$	S	sd	$x/10^{-5}$	S	sd
water	0.365	0.067	0.003	0.437	0.080	0.010	0.658	0.120	0.011	0.869	0.158	0.015
ethanol	0.809	0.046	0.002	1.404	0.079	0.010	2.012	0.112	0.010	3.362	0.185	0.008
2-propanol	1.269	0.055	0.006	2.146	0.092	0.015	3.280	0.139	0.007	4.204	0.176	0.008
acetone	2.366	0.107	0.008	3.678	0.164	0.001	7.578	0.333	0.002	12.525	0.542	0.005
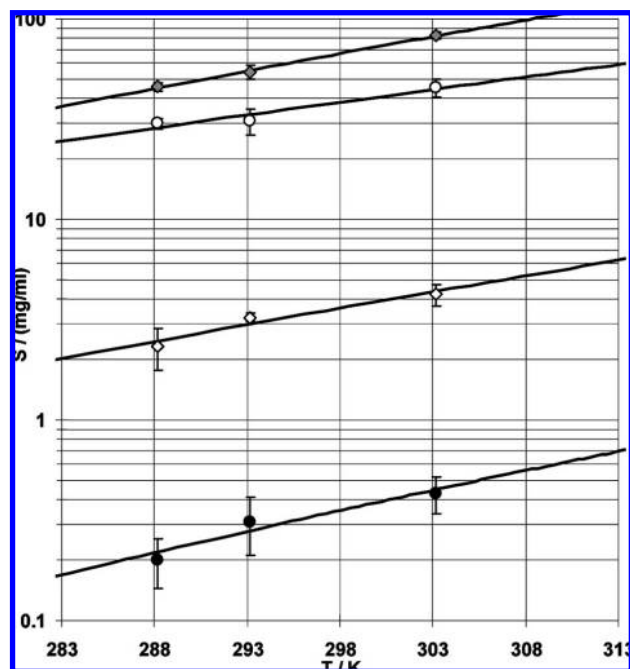
Figure 2. Experimental solubility data for tetracycline base in water (●), ethanol (◆), acetone (○), and 2-propanol (◇). The lines represent modeling using UNIQUAC.

Figure 3. Experimental solubility data for ciprofloxacin base in water (●), ethanol (◆), acetone (○), and 2-propanol (◇). The lines represent modeling using UNIQUAC.

fugacity of component 2 in the solid phase f_2^{S} is equal to the fugacity of the pure solid. The fugacity of component 2 in the liquid phase f_2^{L} can be calculated via the activity coefficient. After introduction into eq 1 we get
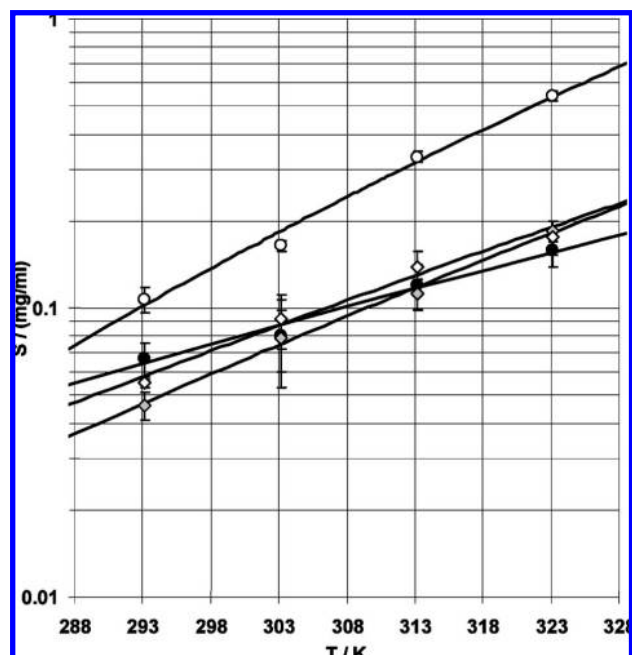
$$x_2\gamma_2(T,P,x_2)f_2^{\text{L}}(T,P) = f_2^{\text{S}}(T,P) \qquad (2)$$

where γ_2 is the activity coefficient of the solute in the liquid phase. Further assumptions lead to the following simplified equation that was used to calculate the mole fraction of the solute in the solvent:

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

T_{mp} is the melting point temperature; $\Delta_{\text{fus}}H$ is the enthalpy of fusion. A more detailed derivation of eq 3 can be found in the literature.[12,13]

Two activity coefficient models were used to calculate the activity coefficients of the solute: NRTL[14] and UNIQUAC.[15] The equations were used as described previously.[11] For the

interaction parameters, τ_{ij}, for NRTL as well as for UNIQUAC, the following temperature dependence was used:

$$\tau_{ij} = a_{ij} + \frac{b_{ij}}{T} \qquad (4)$$

a_{ij} and b_{ij} are adjustable parameters. Unlike the modeling of the hydrochloride forms,[11] where for one system (water + tetracycline·HCl) both a_{ij} and b_{ij} had to be used to give a good representation of the experimental data, for all systems investigated in this work, either the use of a_{ij} or b_{ij} values is sufficient. For some binary systems, especially those where the experimental data cover just a small temperature range, the use of the temperature-independent parameters a_{12} and a_{21} are sufficient. For a better comparison, particularly with systems investigated in part I of this publication, we used parameters b_{ij} for all systems investigated and set parameters a_{ij} equal to zero. For a large number of binary systems, nonrandomness factor α_{12} of the NRTL model varies between 0.20 and 0.47.[13] We set α_{12} to 0.25 for all calculations, being the standard value for the VTPLAN process simulator of Bayer.[16] The values for the
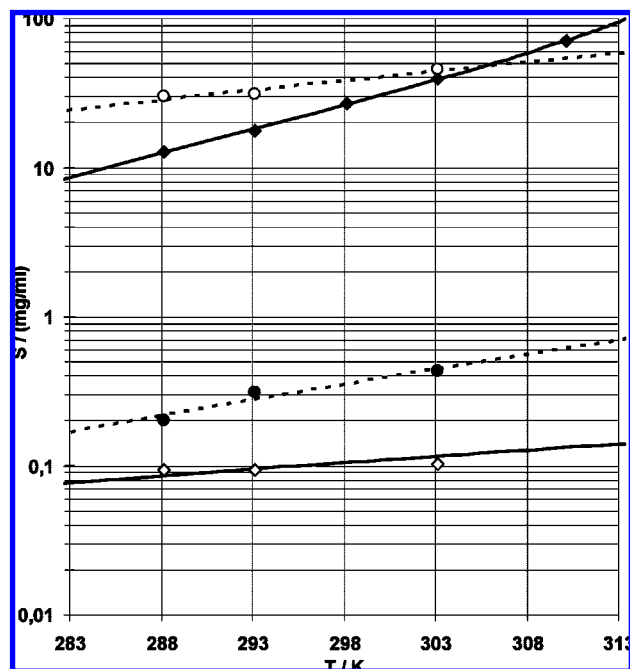
Figure 4. Comparison of the solubility of the base form and hydrochloride form: tetracycline base in water (●) and in acetone (○), tetracycline·HCl in water (◆) and in acetone (◇). Lines represent modeling using UNIQUAC: solid lines are the hydrochloride form, broken lines are the base form.
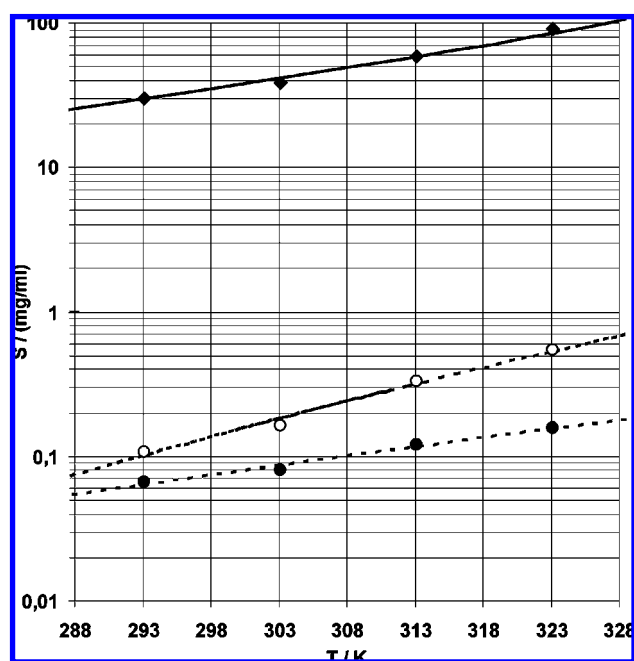
Figure 5. Comparison of the solubility of the base form and hydrochloride form: ciprofloxacin base in water (●) and in acetone (○), ciprofloxacin·HCl in water (◆) and in acetone below the detection limit of 0.01 mg/mL. Lines represent modeling using UNIQUAC: solid lines are the hydrochloride form, broken lines are the base form.

structural parameters r and q of the UNIQUAC model are listed in Table 3. For the solvents, they have been taken from the Dortmund Data Bank.[17] For the antibiotics, the Bondi group contribution method[18] was used to calculate them.

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 for tetracycline was taken from the literature.[19] The experimental determination of the melting temperature of ciprofloxacin is

Table 3. Thermophysical Properties of the Antibiotics and Solvents Used in the Modeling

compd	MW g·mol^{-1}	T_{mp} K	$\Delta_{fus}H$ J·mol^{-1}	ρ kg·m^{-3}	UNIQUAC r	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
ethanol	46.10	159.05	2322.0		2.1055	1.972
2-propanol	60.10	184.65	1498.0		2.7791	2.508
acetone	58.08	178.45	1711.6		2.5735	2.336

challenging since it decomposes during melting. The Merck Index[21] gives a decomposition temperature of 528–530 K. Dorofeev et al.[20] investigated the influence of the heating rate on the melting behavior of fluoroquinolones in a glass capillary apparatus. At a heating rate of 3 K/min decomposition and melting of ciprofloxacin was observed between 530 and 542 K, whereas at a heating rate of 5 K/min it was possible to determine a clear melting interval (538.5–544.6 K). As an input parameter for the solubility modeling we used T_{mp} = 541 K for ciprofloxacin. As compared to the melting point of ciprofloxacin hydrochloride (592.15 K, Merck Index[21]) the value of the base form is 51 K (8.6%) lower. This is the expected behavior, since in almost all cases the hydrochloride forms of organic compounds present behavior of salts. The melting points of organic salts are higher than those of their base form since they also interact by ionic electrostatic forces which are more energetic than those presented among nonionic compounds, such as hydrogen bonding and van der Waals interactions. For tetracycline, the melting point of the base form is 36.5 K (7.6%) higher than that of the hydrochloric form. The values for the melting points of all substances investigated are given in Table 3.

No experimental enthalpies of fusion data were available for any of the antibiotics. These values were calculated using the following relationship:

$$\Delta_{fus}H = T_{mp}\Delta_{fus}S \tag{5}$$

while $\Delta_{fus}S$ was taken to be constant and equal to 56.51 J mol^{-1} K^{-1} as suggested by Gupta and Heidemann.[1] Yalkowsky[2] reported that the entropy of fusion of many drugs and rigid molecules of intermediate size can be estimated by using this value, confirming earlier observations.[22] The calculated melting enthalpies for the antibiotics are reported in Table 3, as well as the pure solvent properties taken from the DIPPR database.[23]

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

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

For the temperature-dependent solvent densities ρ_1, data were taken from the DIPPR database.[23] The apparent liquid density of the solute (antibiotic) ρ_2 was used as a regression parameter. ρ_2 was assumed to be independent of temperature within the investigated temperature range, which lies well below the melting temperature of the antibiotics. Values for ρ_2 are given in Table 3.

The NRTL and UNIQUAC model parameters were obtained by fitting the experimental solubility data. The objective

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

	NRTL model				UNIQUAC model			
solvent	b_{12}	b_{21}	AAD mg/mL	RAE %	b_{12}	b_{21}	AAD mg/mL	RAE %
water	1993.61	2411.71	0.028	8.5	26.36	−224.17	0.023	7.84
ethanol	611.48	−176.35	1.113	1.8	72.15	−317.62	0.766	1.47
2-propanol	881.44	2460.63	0.194	6.0	77.20	−417.83	0.180	5.85
acetone	164.28	2321.04	1.337	4.5	120.88	−432.25	1.495	4.75

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

	NRTL model				UNIQUAC model			
solvent	b_{12}	b_{21}	AAD mg/mL	RAE %	b_{12}	b_{21}	AAD mg/mL	RAE %
water	1767.43	2444.31	0.0375	30.3	−404.19	235.58	0.0036	4.1
ethanol	1465.02	2458.28	0.0066	6.2	−657.59	252.67	0.0033	3.4
2-propanol	1341.11	2476.60	0.0138	9.4	−648.78	265.37	0.0079	6.4
acetone	1448.55	−8.894	0.0164	6.0	−260.08	49.98	0.0106	5.4

function, F, which was used in order to adjust the model parameters, 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

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

The representation of the experimental data with both models is very good. Comparisons of UNIQUAC correlations with the experimental data are shown graphically in Figures 2 and 3. The solubilities of tetracycline cover several orders of magnitude, e.g., at 283.15 K from 0.2 (water) to 45.7 (ethanol) mg/mL. All curves were calculated with two adjustable parameters for each binary system.

The optimized parameters for the two models used to describe the solubility of tetracycline and ciprofloxacin along with the average 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 modeling results of UNIQUAC and NRTL is small. For the ciprofloxacin systems, UNIQUAC with two parameters is better than NRTL with two parameters (α set to 0.25) to describe the temperature dependence of the solubilities, particularly for water. For the tetracycline systems, the difference between the modeling results of UNIQUAC and NRTL is small.

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

The modeling results should be, of course, viewed taking into account that the melting temperature of ciprofloxacin base could not 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 of experimental data, although the temperatures considered were far 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 of the binary interaction parameters b_{ij}. This shall be illustrated with 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 is reduced by 31%. When $\Delta_{fus}H$ is calculated with eq 5 using the 5% higher value for T_{mp}, then the solubility is even 44% lower than the experimental values. When, in a third step, the NRTL parameters b_{12} and b_{21} are optimized, then the representation of the experimental results is almost identical with the calculation using the original values for T_{mp}, $\Delta_{fus}H$, b_{12}, and b_{21}. Though these findings are true for the systems investigated in this work, they cannot be generalized, particularly not when a large concentration range is covered in the modeling. For example, in the moxifloxacin·HCl + water system, a value of $\Delta_{fus}H$ that is 10% lower than the value calculated with eq 5 leads to the occurrence of a maximum in the composition dependence of the activity coefficient.

3.2. COSMO-RS. The COSMO-RS method is a combination of the quantum chemical dielectric continuum solvation model COSMO with a statistical thermodynamics treatment for realistic solvation simulations. It has been found to be extremely helpful in predicting liquid−liquid and vapor−liquid equilibria of mixtures of a wide variety of substances from organic solvents to ionic liquids. It has also been used to predict, at least in qualitative way, the aqueous solubility of complex molecules such as drugs and pesticides.[10,24,25]

However, its application to pharmaceutical compounds is most of the times hindered by the large number of microspecies present in solution that most of the drugs present. In the tetracycline case it is well documented in the literature that in water there are a variety of zwitterionic hydrated forms with different structures, whereas in organic solutions different tautomers and conformers were found according to the solvent.[26-28] These facts made the use of COSMO-RS for the determination of tetracyclines solubilities virtually impossible. On the other hand, ciprofloxacin is an amphoteric API, with four possible microspecies present in aqueous solution, depending on the pH. In the present case the pH was monitored during the solubilization procedure, and its value was found to be equal to 7.5. According to the microspeciation diagram,[29] at this pH more than 90% of the ciprofloxacin is present in its zwitterionic form. In organic solvents ciprofloxacin is neutral. Thus, when using COSMO-RS two microspecies of this drug were considered: the zwitterionic for the water and the neutral for the organic solvents solubility calculations. The COSMOtherm-C2.10105BPSVP parametrization was used.

As found by other authors,[10,24] the pure predictive results obtained by COSMO-RS for the ciprofloxacin were only accurate in relative terms, and the problem was addressed to
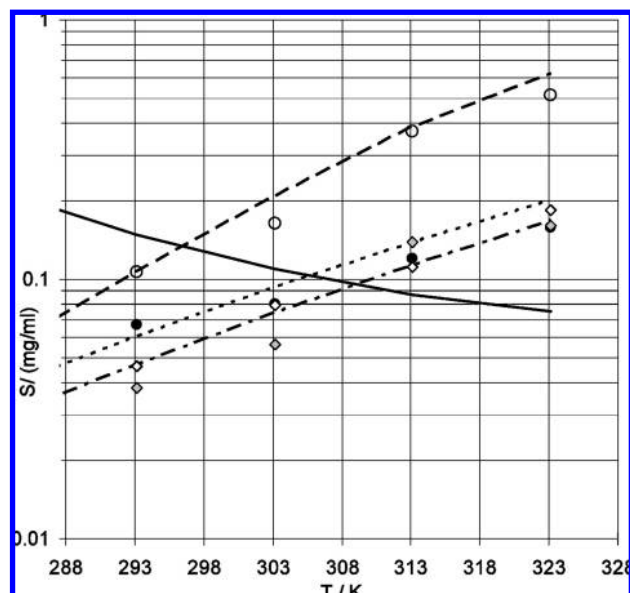
Figure 6. Solubility data for ciprofloxacin base in water (●), ethanol (◆), acetone (○), and 2-propanol (◇) using COSMO-RS, represented by the lines (—) water, (− − −) acetone, (· · ·) 2-propanol, and (− · −) ethanol.

the evaluation of $\Delta_{fus}G$, which in COSMO-RS is done using a QSAR approach with previously specified descriptors. As mentioned before, no experimental fusion data were available for ciprofloxacin, but if $\Delta_{fus}G$ was calculated as suggested by Gupta and Heidemann,[1] much higher (2 orders of magnitude) solubilities of the antibiotic in all the studied solvents were predicted. In fact, the $\Delta_{fus}G$ calculated using QSAR methods presented a very strong temperature dependence, while using and adjusted $\Delta_{fus}G$ to each solubility data point indicated that this parameter was almost temperature-independent but surprisingly quite different from solvent to solvent. If $\Delta_{fus}G$ is taken as an average value of the all obtained values ($\Delta_{fus}G = 5.4$ kcal/mol) the deviations range between 2 and 3 orders of magnitude. Therefore, the procedure adopted in this work is to treat this parameter as an adjustable parameter to each system, including water, and to fix it equal to the value obtained for the experimental solubility data at 313.15 K. The results of the COSMO-RS predictions for the other temperatures for each system are depicted in Figure 6. As can be seen, the model is able not only to capture the solubility sequence for the organic compounds but also provides a fairly good description of the ciprofloxacin solubility in quantitative terms. As for the solubility of ciprofloxacin in water, although the results may not seem very encouraging since COSMO-RS does not predict the correct dependence with temperature, the deviations are smaller than 1 order of magnitude.

4. Conclusions

New experimental data of solubility were obtained for tetracycline and ciprofloxacin in several solvents: water, ethanol, 2-propanol, and acetone. Again, the spectrophotometric method has proved to be an adequate tool for the determination of the solubility of those antibiotics. The solubility of the two studied antibiotics are dependent not only on the solute's properties but also on the solute−solvent interactions. 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 that in the other solvents. As for tetracycline, the solubility order is water < 2-propanol < ethanol ∼ acetone. Surprisingly,

the solubility in 2-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 antibiotic. The solubilities of the hydrochloride forms of the two antibiotics in water are about 2 orders of magnitude higher than those of their base forms. In acetone we see the reverse effect; the solubilities of the base forms are much higher than those of the hydrochloride forms.

The modeling of the SLE data, using NRTL and UNIQUAC, proves that these models can correlate well the solubility of antibiotics for the temperature range for which experimental data are available, with UNIQUAC being, in general, slightly superior to NRTL, when only two adjustable parameters are used for each binary system. The COSMO-RS model presents some limitations in the description of these complex models.

Greek Symbols

γ_2 = activity coefficient of the solute in solution

τ_{ij} = temperature-dependent binary interaction parameter

ρ_1 = density of the solvent

ρ_2 = apparent liquid density of the solute

ρ_M = density of the solution

Superscripts

S = solid

L = liquid

Subscripts

fus = fusion

model = value calculated with the model

exp = experimental value

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