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Phase Equilibria of the System Drug + Water

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ABSTRACT: The production and the application of pharmaceuticals customarily involve liquid solvents for reaction, separation, and formulation. In pharmaceuticals, poor water solubility and slow dissolution into the gastrointestinal tract are major obstacles for releasing new dosage forms into the market. These issues have been responsible for the rejection of 70 % of the potentially active drugs. In this experimental study devoted to the phase behavior of three binary systems made from drug (S-(+)-2-(4-(2-methylpropyl) phenyl) propanoic acid [ibuprofen], (2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol [farnesol], and ((R)-(6-methoxyquinolin-4-yl)((2S,4S,8(R)-8-vinylquinuclidin-2-yl)methanol [quinine]) and pure water. Beside the solubility in water (solid−liquid equilibrium, SLE), also the miscibility gaps (LLE) of two systems, namely (2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol + water and (S)-2-(4-(2-methylpropyl)phenyl)propanoic acid + water, were measured applying the equilibrium method in combination with different analytical methods, like Karl Fischer titration, HPLC, and UV−vis spectroscopy. From the solubility data, the heat of fusion of the studied drugs could be extracted. An important factor which can have a significant impact on the thermodynamic data is the type of the investigated isomer.

INTRODUCTION

The prediction of the aqueous solubility of drug candidates may not be a primary concern in early screening stages, but the knowledge of the thermodynamic properties in terms of phase behavior of drug candidates is of paramount importance in assisting the discovery, as well as the development, of new drug entities at later stages. The applications of newly developed drugs are frequently limited by their solubility in preferential solvent water. For this reason drug formulations, like addition of surfactant, encapsulation in polymer particles, or use of hydrogels, are applied. For the optimization of such formulation regarding the drug loading capacity and the drug release a theoretical tool will be desirable. In principal thermodynamicis of such a complex system can be used for the development of such a tool. The necessary precondition is the knowledge of the solubility of drugs in water as a function of temperature and composition and the development of thermodynamic models for the calculation of the involved phase behavior.

In 1997, Lipinski et al.[1] reviewed distinctly different but complementary experimental and computational approaches to estimate solubility and permeability in drug discovery and drug development settings. The computational approaches are mainly based on empirical correlations,[1,2] on activity coefficient models,[3−7] or on molecular descriptors.[1,8−12] Another possibility for the prediction of the solubility in water or in other solvents is the application of group contribution methods.[13−15] Faller and Ertl[16] summarized the available models and focused on the value which can be extracted by comparing calculated and measured solubility, discussed the potential and limitations of the main computational approaches, and provided guidelines as to when to trust the computed value. Recently,[17−19] equations of state were applied in order to model the solid−liquid equilibria (SLE) of drugs in water. It was found that with this simplified approach, the temperature dependence of the solubility was not successfully correlated in many cases in contrast to the approach that explicitly accounts for the complex hydrogen bonding interactions.[17] The main reason for this is the use of combining rules for the calculation of parameters for the cross hydrogen bonding interactions between the solute and solvent molecules. In order to achieve an excellent agreement between the experimental data and the modeling results, a binary interaction parameter must be fitted.[17] Another approach in this field is the prediction of pharmaceutical molecules in solvents or solvent mixtures which consists of the application of perturbed-chain-statistical association theory.[20,21] In order to achieve a high quality, some parameters must be fitted to experimental data. Beside the SLE, some drugs show also a miscibility gap in water (LLE), which can not be predicted in the moment. For these reasons, experimental data are still necessary.

Although a large experimental effort for the measurement of thermodynamic data of pharmaceutical molecules (i.e., refs 22−50) was released in the last years, the experimental database is still limited, even for the binary subsystem drug + water.[51] Exhaustive compilations of experimental results are covered elsewhere.[24,52]

Even more, experimental data for the same physical property and at the same conditions may vary significantly from one source to another. An additional characteristic feature of pharmaceutical molecules that is expected to affect modeling of their solubilities is polymorphism. Drugs may crystallize in many different forms, where each form has different fusion properties,

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Table 1. Literature Survey of Physical Properties of (RS)-2-(4-(2-Methylpropyl)Phenyl)Propanoic Acid

property	value	isomer	T / K	pH value	source
pK_a at I^a = 0.018 mol·L^{-1}	4.38	unknown	298.15		37
pK_a at I = 0.003 mol·L^{-1}	4.51	unknown	310.15		37
$\Delta_{sub}H$/(kJ·mol^{-1})	115.8	±			26
$\Delta_{sub}H$/(kJ·mol^{-1})	197.4	S (+)			26
T_M/K	347.15	±			26
T_M/K	348.15 - 350.15	±			60
T_M/K	344	±			25
T_M/K	323.15	S (+)			26
T_M/K	326.15 - 328.15	S (+)			60
T_M/K	326.15 - 328.15	S (+)			60
T_M/K	319	S (+)			25
T_M/K	319.5	R (−)			25
T_M/K	310	eutectic mixture			25
T_M/K	349.2	unknown			58
T_M/K	347.15	unknown			22
$\Delta_{fus}H$/(kJ·mol^{-1})	23.1	±			26
$\Delta_{fus}H$/(kJ·mol^{-1})	27.87	±			60
$\Delta_{fus}H$/(kJ·mol^{-1})	26.9	±			25
$\Delta_{fus}H$/(kJ·mol^{-1})	17.9	S (+)			26
$\Delta_{fus}H$/(kJ·mol^{-1})	17.9	S (+)			60
$\Delta_{fus}H$/(kJ·mol^{-1})	19.7	S (+)			25
$\Delta_{fus}H$/(kJ·mol^{-1})	17.9	R (−)			60
$\Delta_{fus}H$/(kJ·mol^{-1})	25.5	unknown			22
solubility[b]	$5.7 \cdot 10^{-5}$	±	310.15	4.5	60
solubility	$4.97 \cdot 10^{-3}$	±	310.15	7.7	60
solubility	$1.94 \cdot 10^{-4}$	±	298.15	1.5	25
solubility	$4.8 \cdot 10^{-5}$	S (+)	310.15	4.5	60
solubility	$5.94 \cdot 10^{-3}$	S (+)	310.15	7.7	60
solubility	$3.69 \cdot 10^{-4}$	S (+)	298.15	1.5	25
solubility	$3.69 \cdot 10^{-4}$	R (−)	298.15	1.5	25
solubility	$4.0 \cdot 10^{-4}$	eutectic mixture	298.15	1.5	25
solubility	$6.9 \cdot 10^{-6}$	unknown	278.15	2	58
solubility	$8.8 \cdot 10^{-6}$	unknown	298.15	2	58
solubility	$1.1 \cdot 10^{-5}$	unknown	298.15	7.4	22
solubility	$4.9 \cdot 10^{-5}$	unknown	298.15	low	59
solubility	$2.1 \cdot 10^{-5}$	unknown	298.15		52
solubility	$1.55 \cdot 10^{-5}$	unknown	303.15	7.4	22
solubility	$2.05 \cdot 10^{-5}$	unknown	308.15	7.4	22
solubility	$5.21 \cdot 10^{-5}$	unknown	310.15	2	58
solubility	$2.64 \cdot 10^{-5}$	unknown	313.15	7.4	22

[a] I means ionic strength. [b] Solubility in weight fraction, sometimes recalculation was performed assuming the density of the liquid phase is 1 g·cm^{-3}.

which renders the experimental determination and the modeling of solubility a nontrivial procedure. During solubility measurement, a compound may transform to a more-stable polymorph. Surface-active compounds, when dissolved in water to saturation, can form self-associated aggregates which can complicate the interpretation of the aqueous solubility data. In many studies dealing with the experimental measurements of solubilities, the crystalline structure of the material is not investigated. Many drug compounds contain at least one acid and/or basic functionality, and the ionization state of these groups plays an important role in determining the physicochemical properties. Acid dissociation constants (pK_a values) are useful physicochemical measurements describing the extent of ionization of functional groups with respect to pH.[53−55] The problem arising in the experimental estimation of this quantity is the very low solubility in water; therefore, the experiments were performed in the presence of an organic solvent, mostly methanol, and extrapolated using a regression model based on the mass action law. Several drugs hold a chiral center and form optical isomers. This situation has also an impact on the physical properties of the drugs. Last but not least, the solubility is often very low reaching the sensitivity of the analytical methods.

This contribution focused on the experimental investigation of the phase behavior including solid−liquid and liquid−liquid equilibria of pharmaceutical substances (component 1) in water (component 2) for three examples, namely (2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol (quinine), (S-(+))-2-(4-(2-methylpropyl) phenyl)propanoic acid (ibuprofen), and (R)-(6-methoxyquinolin-4-yl)((2S,4S,8(R)-8-vinylquinuclidin-2-yl) methanol (farnesol).

LITERATURE REVIEW

(RS)-2-(4-(2-Methylpropyl)Phenyl)Propanoic Acid. (RS)-2-(4-(2-Methylpropyl)phenyl)propanoic acid (ibuprofen) is a nonsteroidal anti-inflammatory drug derivative of propionic acid used widely as an analgesic and as an antipyretic, and it is also used for relief of symptoms of rheumatoid arthritis and osteoarthritis, in addition to treatment of dysmenorrheal. The selected physical properties of (RS)-2-(4-(2-methylpropyl)-phenyl)propanoic acid found in the literature are collected in Table 1; however, only values given in tables or in text and not read off in figures were used. Caused by the chiral center of the (RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid molecule, two enantiomers exists. The racemic compound contains an equal number of molecules of each enantiomer in the unit cell of the crystal. Ertel at al.[28] studied the vapor pressure of ibuprofen at different temperatures using the effusion method. Perlovich et al.[26] were able to confirm these values applying the transpiration method. In both papers[26,28] no traces of the decomposition product could be found, where the material was heated until 345 K.

Since most drugs, and particularly the anti-inflammatories studied here, are sparingly soluble in water, the literature pK_a values were often determined potentiometrically in mixtures of water and an organic solvent, to obtain a suitable solubility.[37] The pK_a values have been successfully fitted to a general equation based on the mass action law derived to explain the variation of the dissociation constant of an acid with solvent composition in binary solvent mixture.[37] The parameters of the regression model obtained allow to study the effect of preferential solvation of the drugs on the pK_a value, and to estimate the aqueous pK_a value from pK_a values measured in binary solvents of different composition. However, the literature shows a dispersion of aqueous pK_a values ranging from 4.14 to 4.64.[37]

Melting points as well as enthalpies of fusion can be measured with DSC. The data given in Table 1 show the large influence of isomer on these properties. Perlovich et al.[26] investigated the sublimation, crystal lattice energies, and crystal structures of racemates and enantiomers of S (+)- and (±)-ibuprofen using X-ray diffraction, thermoanalysis, and crystal energy calculations. Although the S (+) enantiomer of ibuprofen is the only pharmacologically active molecule, the racemate is almost as active in vivo because the S (+) enantiomer is continuously formed metabolically from R (−) enantiomer.[56]

Dwievedi et al.[25] constructed a binary phase diagram with the help of DSC curves of (RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid using (R)-2-(4-(2-methylpropyl)phenyl)propanoic acid, (S)-2-(4-(2-methylpropyl)phenyl)propanoic acid, and (RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid. The phase diagram was typical of a eutectic system with additional compound formation.[25] Powder X-ray diffraction analysis showed that USP-ibuprofen was a racemic compound, capable of existing as a separate phase independent of its constituent enantiomers, and not a racemic mixture.[25] If a racemic compound remains completely undissociated upon melting, the dystectic point occurs as a sharp maximum in the phase diagram where the two liquidus curves appear to intersect. On the other hand, if the racemic compound dissociates, the products of dissociation, namely, the constituent enantiomers, depress the melting point. The two liquidus curves in the dystectic region become rounded as a result, and merge into each other forming one continuous flattened curve. The degree or rounding off will vary depending on the degree of dissociation. Dwievedi et al.[25] could not detect a sharp maximum in the phase diagram indicating that (RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid is largely dissociated in the liquid state.

Many nonsteroidal anti-inflammatory drugs,[57] such as 2-{1-[(4-chlorophenyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid (indomethacin), 2-(2-(2,6-dichlorophenylamino)phenyl)acetic acid (diclofenac), (RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid, (RS)-2-(3-benzoylphenyl)propanoic acid (ketoprofen), (+)-(S)-2-(6-methoxynaphthalen-2-yl) propanoic acid (naproxen), and {(1Z)-5-fluoro-2-methyl-1-[4-(methylsulfinyl)benzylidene]-1H-indene-3-yl}acetic acid (sulindac), can self-associate by forming mixed-charge micelle or micelle-like structures. Fine et al.[57] figured out that ibuprofen solubilized the azo-dye only in the presence of high ionic strength. This situation can be interpreted that no micelle formation in pure water occurs. The solubility of (RS)-2-(4-(2-methylpropyl) phenyl)propanoic acid depends on the isomer, slightly on temperature, and strongly on pH value (Table 1), where pH 7.4 corresponds to the physiological value.

Fini et al.[58] measured the water solubility at three different temperatures (278.15 K, 298.15 K, and 310.15 K), where the solutions were buffered at pH 2.0, so that only the undissociated species were present. However, no statement about the selected isomer is given.[58] The reduction of solubility by a salting out effect due to the increasing ionic strength must be considered.[57] Additionally, the aging of the drug must be taken into account.[59] Solid phases generated by precipitation are often metastable and can lead to the formation of supersaturated solutions with slow precipitation kinetics.[59] High throughput solubility measurements obtained by diluting DMSO stock solutions into aqueous buffer lead to solubility data that can be increased in a highly compound dependent way compared to shake-flask solubility values.[42]

Avdeef et al.[59] compared the results of a normal saturation shake-flask method to a new potentiometric acid−base titration method for determining the intrinsic solubility and the solubility−pH profiles of ionizable molecules, and reported the solubility constants determined by the latter technique. For ibuprofen a value for the intrinsic solubility of 49 $\mu g \cdot mL^{-1}$ was obtained.[59] Unfortunately, no temperature is specified. The solubility depends strongly on pH value. For example, for low pH values (lower than 4), the solubility is between 10^{-3} and 10^{-4} $mol \cdot L^{-1}$ (Figure 1 in ref 59) and at pH values higher than 9 the solubility increases strongly reaching a value closed to 1 $mol \cdot L^{-1}$ (Figure 1 in ref 59). For pH > 7 the precipitation of the sodium salts of weak acids can be occur, if additional salt in order to control the pH value is added.[59]

It is generally recognized that formulating (RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid is difficult and relies mainly on the expertise of the formulator. Caused by the low solubility, several formulations containing (RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid were discussed in the literature.[61−85]

In this study, not only the solubility in water (SLE) without a buffer as a function of temperature has been performed but also the LLE at higher temperatures.

(R)-(6-Methoxyquinolin-4-yl)((2S,4S,8(R)-8-Vinylquinuclidin-2-Yl)Methanol. (R)-(6-Methoxyquinolin-4-yl)((2S,4S,8-(R)-8-vinylquinuclidin-2-yl)methanol (quinine) is a natural white crystalline alkaloid having antipyretic, antimalarial, analgesic, anti-inflammatory properties, and a bitter taste. Quinine contains two major fused-ring systems: the aromatic quinoline and the bicyclic quinuclidine. The most important medical application is the treatment of malaria.[86] The presence of Aloe Vera within the formulation containing colchicine, or oxybutynin or quinine provided enhancements for the skin permeation.[87]

pK_a was measured using electrophoresis yielding a value of 4.29.[55] The apparent acid dissociation constants of quinine were determined pH-metrically in different mixtures made from organic component and water.[54] Using the Yasuda-Shedlovsky extrapolation the acid dissociation constants in water (8.59) was derived.[54] There exists only a few data points related to the solubility of quinine in water[88−90] however these values ranging from $5.7 \cdot 10^{-4}$ to $5.7 \cdot 10^{-3}$ (weight fraction) at comparable temperatures. The solubilization of quinine was also studied.[91,92] In this contribution the solubility in pure water as function of temperature is measured.

(2E,6E)-3,7,11-Trimethyldodeca-2,6,10-trien-1-ol. (2E,6E)-3,7,11-Trimethyldodeca-2,6,10-trien-1-ol (farnesol) is a natural organic compound which is an acyclic sesquiterpene alcohol found as a colorless liquid. Farnesol is present in many essential oils and it is used in perfumery to emphasize the odors of sweet floral perfumes. Additionally, farnesol is a natural pesticide for mites and is a pheromone for several other insects. Recently, the application of farnesol for enhancement of the permeation of oil−water interface in drug formulations was discussed.[93,94] From the pharmaceutical point of view farnesol signalized antibacterial and antifungal properties.[95] Ginger et al.[96] discussed to preparation of polymer microparticles containing farnesol. To the best to our knowledge no thermodynamics data in terms of phase equilibria are available in the literature. For this reason we measured to liquid−liquid equilibria of farnesol in pure water.

EXPERIMENTS

Materials. All compounds were purchased from commercial sources. The three drugs are characterized in Table 2 and the chemical structure is given in Figure 1. All materials were used as received without further purification.

Methods. *SLE Measurements.* A number of useful experimental methods are reviewed, including the miniaturized shake-flask microtiter plate, the micro solubility self-calibrating direct

Table 2. Used Drugs

drug	CAS	M / g·mol^{-1}	purchaser	purity in w_1 / g·g^{-1}
(S)-2-(4-(2-methylpropyl) phenyl)propanoic acid	15687-27-1	206.27	Fluka	>0.99
(R)-(6-methoxyquinolin-4-yl)((2S,4S,8(R) - 8-vinylquinuclidin-2-yl)methanol	130-95-0	324.41	Sigma-Aldrich	>0.98
(2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol	4602-84-0	222.36	Sigma-Aldrich	>0.95

UV, potentiometric, and the micro dissolution methods.[12] The measurement of the solubility is challenging when highly insoluble substances are considered exceeding the sensitivity of the analytical method. Solubility measurement under equilibrium conditions is largely a labor-intensive but straightforward procedure.

Classical approaches for measuring solubility are based on the saturation shake-flask method. In brief, accurately known masses of drug ((S)-2-(4-(2-methylpropyl)phenyl)propanoic acid or (R)-(6-methoxyquinolin-4-yl)((2S,4S,8(R)-8-vinylquinuclidin-2-yl)methanol) were weighted out directly into tightly sealed vials containing pure water and stirred in a thermostat at the desired temperature. Samples were withdrawn using 0.44 mm filter (folded filter for quantitative analysis; Macherey - Nagel, Germany). The vials were put in a thermostat at a selected temperature for two weeks to reach saturation. Every day a sample was taken out of the vial using a microsyringe. In order to avoid precipitation during temperature change the solution were diluted using a known amount of ethanol. The concentration in equilibrium was measured using UV−vis spectroscopy (Specord 200, Analytik Jena, Germany). Before the equilibrium concentration was measured the influence of ethanol on the absorption spectra was investigated. For this purpose several solutions containing aqueous solution of drug with a known drug concentration as well as solutions with the same drug content, but dissolved in a water ethanol mixture. In the case of (S)-2-(4-(2-methylpropyl)phenyl)propanoic acid, it was figured out that the absorption at a wavelength of 225 nm is not influenced by the ethanol present in the mixture. In the case of (R)-(6-methoxyquinolin-4-yl)((2S,4S,8(R)-8-vinylquinuclidin-2-yl)methanol the absorption spectra in the wavelength range between 295 and 310 nm range can be used for the determination of the concentration. For both drugs a calibration curve was established by the measurement of the absorption spectra for careful prepared solutions with known drug content. For (S)-2-(4-(2-methylpropyl)phenyl)propanoic acid, the adsorptions at a wavelength of 225 nm were direct use for plotting the calibration curve. The correlation coefficient of the obtained straight line was 0.9987. For (R)-(6-methoxyquinolin-4-yl)((2S,4S,8(R)- 8-vinylquinuclidin-2-yl)methanol, the calibration curve for the determination of the (R)-(6-methoxyquinolin-4-yl)((2S,4S,8(R)- 8-vinylquinuclidin-2-yl)methanol content was found out by integrating the absorption in the range between 295 and 310 nm for measured solution with known (R)-(6-methoxyquinolin-4-yl)-((2S,4S,8(R)-8-vinylquinuclidin-2-yl)methanol content, resulting in a straight line with a correlation coefficient of 0.9997.

All experiments were carried out 3-fold. Within the experimental accuracy all three measurements lead to the same value.

LLE measurements. The binary systems (S)-2-(4-(2-methylpropyl)phenyl)propanoic acid + water as well as (2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol + water show a large miscibility gap, where a water-rich phase with a small amount of drug

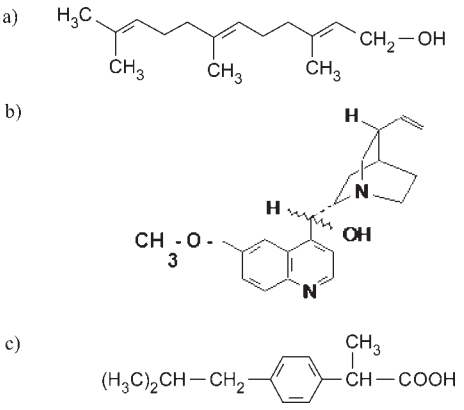

Figure 1. Chemical structures of the studied drugs (a) (2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol, (b) (R)-(6-methoxyquinolin-4-yl)(-(2S,4S,8(R)-8-vinylquinuclidin-2-yl)methanol, and (c) (RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid).

coexists with an organic phase with a small amount of water. According the data given in Table 1 the melting point of (S)-2-(4-(2-methylpropyl)phenyl)propanoic acid is higher than 319 K and hence at higher temperatures a miscibility gap instead of the SLE will be developed. The cloud point temperature of the water-rich side of the phase diagram was measured by visual observation. For this purpose homogeneous solutions with different amount of (S)-2-(4-(2-methylpropyl) phenyl)propanoic acid were prepared at higher temperatures. These solutions were slowly cool down and the formation of the second phase were observed. In order to make sure that the equilibrium is found, the solutions were heated very slowly again and the temperatures at which the coexisting phase disappears were recorded. Both temperatures were within 0.25 K identical.

For the measurement of the equilibrium concentration for the system (2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol + water a different procedure was applied. Excess amounts of liquid (2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol are placed into vials containing pure deionized water. The vials are sealed and placed into a constant temperature bath for 24, 48 h, or longer, until equilibrium is evident. The equilibrium could be recognized via two clear solutions separated by a sharp interface. Usually the equilibrium was reached within one day. A small sample of the water-rich phase was taken and afterward the concentration of (2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol were measured with the help of HPLC (model HP 1100 Series, Hewlett-Packard, USA). This analyzing method was suggested by Villa et al.[97]

The HPLC-apparatus is equipped with C18 column (ChromSa (250 × 4.6 mm)) filled with Zorbax Pro (10/60, 10 μ) purchased by M&W Chromatographietechnik GmbH, Germany. For the detection the UV−vis absorption is used. In

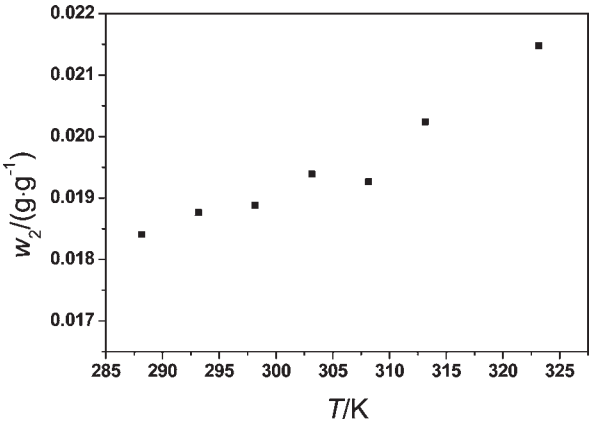

Figure 2. Experimental weight fraction of water ($w_2/(g\cdot g^{-1})$) in the (2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol-rich phase as function of temperature (T/K) measured with Karl Fischer titration.

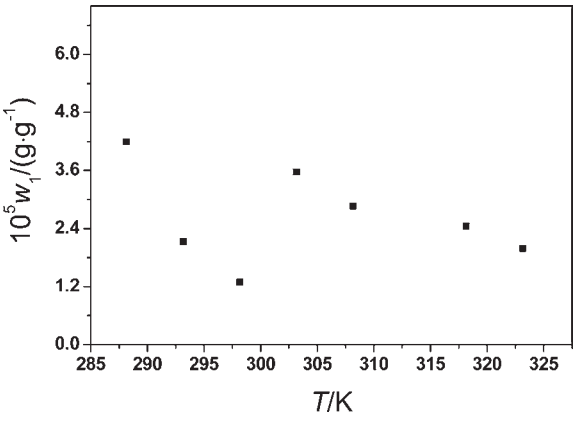

Figure 3. Experimental weight fraction of (2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol ($w_1/(g\cdot g^{-1})$) in the water-rich phase as function of temperature (T/K) measured with HPLC method.

order to avoid demixing ethanol were added to the samples. In preliminary experiments the influence of ethanol on the chromatogram and a suitable wavelength for the calibration were estimated. At a wavelength of 210 nm no influence of ethanol could be found and therefore this wavelength was used for the construction of the calibration line. The obtained correlation coefficient was 0.999.

For both systems the water concentration in the organic phase was measured in the same way like described above; however the water content was estimated with the help of Karl Fischer titration (AE 260, Mettler-Toledo, Germany).

All experimental data are collected in the Appendix.

RESULTS AND DISCUSSION

System (2E,6E)-3,7,11-Trimethyldodeca-2,6,10-trien-1-ol + water. (2E,6E)-3,7,11-Trimethyldodeca-2,6,10-trien-1-ol (farnesol) is at room temperature a colorless liquid and hence the SLE can be found at low temperatures. Caused by the chemical nature of (2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol it is not complete miscible with water. This system forms a large miscibility gap. The water concentration in the (2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol-rich phase increased slightly with increasing temperature (Figure 2).

The (2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol weight fractions in the water-rich phase are depicted in Figure 3 as function of temperature. Within the experimental accuracy the (2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol concentration does not depend on temperature. The relatively high experimental error is caused by the very low solubility reaching the limit of sensitivity of the analytical method.

System (RS)-2-(4-(2-Methylpropyl)Phenyl)Propanoic Acid + Water. In the literature[25,26,60] exist three different melting temperatures for (S)-2-(4-(2-methylpropyl)phenyl)propanoic acid, namely 319 K,[25] 323.15 K,[26] and 326.15 to 328.15 K.[60] In the binary system made from water and (S)-2-(4-(2-methylpropyl)phenyl)propanoic acid will be a SLE below the melting point and a LLE above the melting point. The phase diagram shown in Figure 4 tends rather to 319 K than to 326.15 K as melting temperature for the pure drug. Caused by the more polar character of (S)-2-(4-(2-methylpropyl)phenyl)propanoic acid in comparison with (2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol the drug concentration in the water-rich phase is increased by 1 order of magnitude. In contrast to the data for the system water + (2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol (Figure 3), the temperature has a larger impact on the solubility for (S)-2-(4-(2-methylpropyl)phenyl)propanoic acid than for (2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol.

During our measurement no buffer was used. For this reason the pH value should be closed to the pK_a value, but the pK_a value depends on temperature as well as on the ionic strength (Table 1). It is very hard to compare our own data with values given in the literature or in Table 1, because the solubility depends at the same temperature also on the pH value and on the used isomer. For the studies isomer only 3 data points exist. At 310.15 K and pH 4.5 Romero et al.[60] found for the weight fraction of the drug $w_1 = 4.8 \cdot 10^{-5}$ $g\cdot g^{-1}$. Our experiments results in a value of $w_1 = 1.6 \cdot 10^{-4}$ $g\cdot g^{-1}$. Generally, the solubility decrease with decreasing pH value.[12,59] At pH 1.5 and T = 298.15 K Dwivedi et al.[25] measured a solubility of $w_1 = 3.69 \cdot 10^{-4}$ $g\cdot g^{-1}$. The reason for this situation can not be clarified. Analyzing the obtained spectra no hint for degradation or other chemical reaction could be recognized. If aging of the drug occurs than the solubility should be decrease.[60] We have taken a sample every day, but we were not able to see any long-term effect. Using DSC experiments it was found that the samples melted over a narrow temperature range, and the DSC curve exhibit structure-making peaks, probably due to some polymorphism.[58]

The solubility data given in Figure 4 were treated based one linear solubility−temperature relationship according the van't Hoff plot (Figure 5). The data plotted in this figure gives only approximately a straight line. This situation can be interpreted as the influence of the activity coefficients, which are quite large for this mixture. For ideal solutions the solubility depends on the nature of the solid and is not affected by the nature of the solvent. For real solutions, especially for solute in solvents with a very low solubility, the solubility generally depends more on its affinity to the solvent rather than on the structure of the solid state, even though the solution is very diluted. Assuming an ideal behavior of the liquid mixture leads to a drug solubility of $w_1^L \approx 0.02$ $g\cdot g^{-1}$ depending on the used melting temperature and enthalpy of fusion. Theoretically the heat of fusion can also depend on temperature. However; having in mind the small temperature range, this effect should not be dominant. The slope of this straight line yields the enthalpy of fusion for the solute, which is

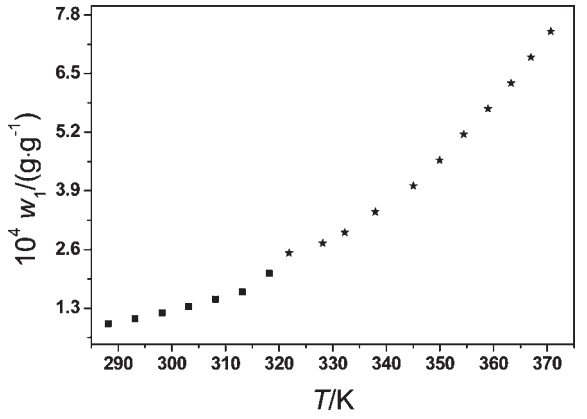

Figure 4. Phase behavior of diluted (S)-2-(4-(2-methylpropyl)phenyl)-propanoic acid solutions (solid squares: SLE, stars: LLE), where w_1-$(g{\cdot}g^{-1})$ is the weight fraction of the drug and T/K the temperature.

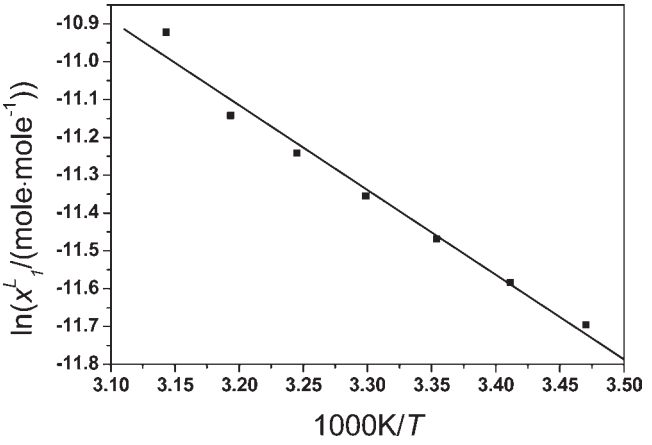

Figure 5. van't Hoff plot for aqueous (RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid solutions (squares: experimental data, line: fitted line), where $x_1^L/(\text{mole}\cdot\text{mole}^{-1})$ is the mole fraction of the drug and T/K is the temperature.

generally assumed to be independent of temperature. The enthalpy of fusion for (S)-2-(4-(2-methylpropyl)phenyl)-propanoic acid is 18.6 kJ·mol^{-1}. This value is close to the values given in the literature[25,26,60] or in Table 1 but differ markedly from the often used value of 25.5 kJ·mol^{-1}.[15,21] The later one is only valid approximately (see Table 1) if a racemate mixture is considered.

At temperatures higher than the melting point of pure (S)-2-(4-(2-methylpropyl)phenyl)propanoic acid a liquid−liquid phase split in the system (S)-2-(4-(2-methylpropyl)phenyl)-propanoic acid + water can be found. The concentration of water in the organic phase is plotted in Figure 6 as function of temperature. Increasing temperature leads to more water in the organic phase. To the best of our knowledge no such data are available in the literature. Caused by the higher polarity of (S)-2-(4-(2-methylpropyl) phenyl)propanoic acid in comparison with (2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol the water weight fraction in the organic phase is higher in the (S)-2-(4-(2-methylpropyl)phenyl)propanoic acid-rich phase than in the (2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol-rich phase.

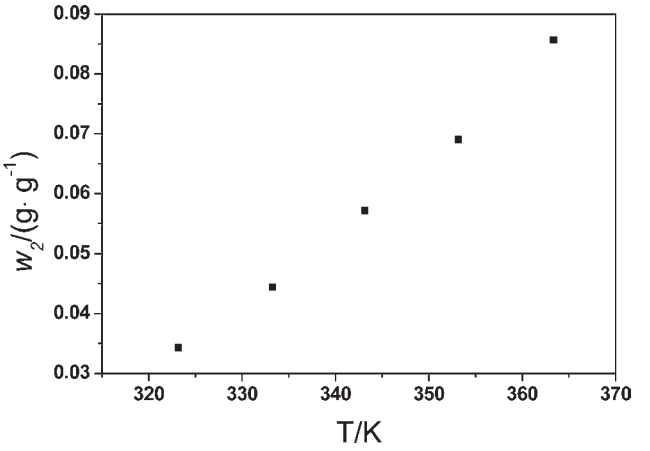

Figure 6. Water content $(w_2/(g{\cdot}g^{-1}))$ of the organic phase for the system (S)-2-(4-(2-methylpropyl)phenyl)propanoic acid + water as function of temperature (T/K).

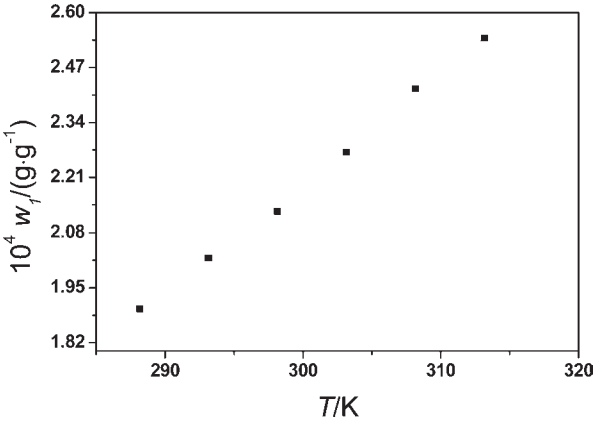

Figure 7. Experimental solubility of (R)-(6-methoxyquinolin-4-yl)-((2S,4S,8(R)-8-vinylquinuclidin-2-yl)methanol $(w_1/(g{\cdot}g^{-1}))$ in water at different temperatures (T/K) obtained by UV−vis spectroscopy.

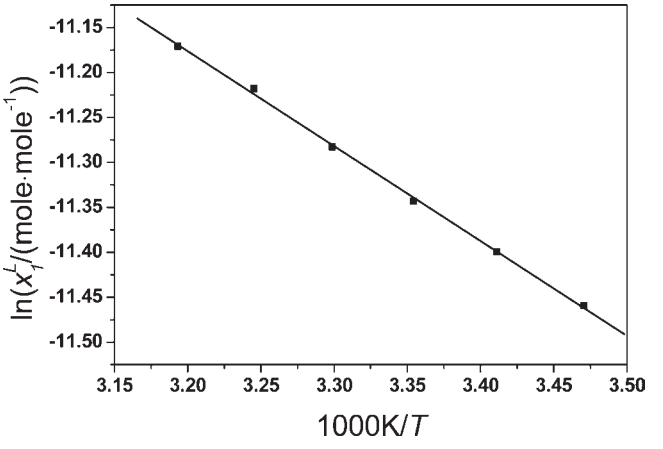

Figure 8. van't Hoff plot for aqueous (R)-(6-methoxyquinolin-4-yl)-((2S,4S,8(R)- 8-vinylquinuclidin-2-yl)methanol solutions (squares: experimental data, line: fitted line), where $x_1^L/(\text{mole}\cdot\text{mole}^{-1})$ is the mole fraction of the studied drug and T/K the temperature.

System (R)-(6-Methoxyquinolin-4-yl)((2S,4S,8(R)- 8-Vinylquinuclidin-2-yl)Methanol + Water. The experimental data

related to the solubility of (R)-(6-methoxyquinolin-4-yl)-((2S,4S,8(R)-8-vinylquinuclidin-2-yl)methanol in water are depicted in Figure 7: The solubilities increase nearly linearly with increasing temperature. In this work the obtained drug solubility at 293.15 K is $w_1 = 2.02 \cdot 10^{-4}$ g·g^{-1}. At the same temperature Müller[89] found a value of $w_1 = 57.4 \cdot 10^{-4}$ g·g^{-1}. However; at 298.15 K the value in this work is small than the value given in the literature[89] ($w_1 = 57.4 \cdot 10^{-4}$ g·g^{-1}). (R)-(6-Methoxyquinolin-4-yl)((2S,4S,8(R)-8-vinylquinuclidin-2-yl)methanol has a asymmetric carbon atom and hence it should form also optical isomers, which can lead to differences in their solubility. Maybe, some different isomers are used for the experiments. Unfortunately, it is not known which isomer is used in this study or in the cited literature.

Similar to Figure 5 for the system water + (S)-2-(4-(2-methylpropyl)phenyl)propanoic acid, the experimental data for the system (R)-(6-methoxyquinolin-4-yl)((2S,4S,8(R)- 8-vinylquinuclidin-2-yl)methanol + water were plotted according van't Hoff law in Figure 8. The slope of the fitted line leads to a heat of fusion of (R)-(6-methoxyquinolin-4-yl)((2S,4S,8(R)- 8-vinylquinuclidin-2-yl)methanol of 8.8 kJ·mol^{-1}.

CONCLUSION

Water solubility plays a key role in areas such as drug dosage, anesthesiology, corrosion of metals, transport fate of pollutants in terrestrial, aquatic and atmospheric ecosystems, deposition of minerals and composition of ground waters, and availability of oxygen and other gases in life support systems. Reliable measurements of the solubility of drugs especially of ionizable molecules offer significant challenges. Beyond discovery, at the preformulation stage, among the first physicochemical parameters to be carefully measured is often the solubility. Solubility data are needed for development of parenteral formulations for use in early animal bioavailability and toxicity studies. Later in development, solubility takes on a broader focus: salt selection, rate of drug dissolution, and stability of the dosage form depend in important ways on the solubility of the candidate molecules.

The three different drugs show three different types of binary phase behavior in the temperature range of interest. (2E,6E)-3,7,11-Trimethyldodeca-2,6,10-trien-1-ol shows a liquid−liquid phase split in the investigated temperature range. The phase behavior of (S)-2-(4-(2-methylpropyl)phenyl)propanoic acid can by characterized by liquid−liquid and solid−liquid equilibrium. The heat of fusion of (S)-2-(4-(2-methylpropyl)-phenyl)propanoic acid can be extracted from the experimental data. This quantity depends strongly on the composition of (RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid (eutectic or racematic mixture or pure enantiomers). Our finding is partly very close to the literature value.[4] For the aqueous solution of (R)-(6-methoxyquinolin-4-yl)((2S,4S,8(R)-8-vinylquinuclidin-2-yl)methanol only liquid−solid equilibrium was measured. The solubility data for (R)-(6-methoxyquinolin-4-yl)((2S,4S,8(R)- 8-vinylquinuclidin-2-yl)methanol are located within the scattered data in the literature.[88−90] It can be speculated that the physical properties of (R)-(6-methoxyquinolin-4-yl)((2S,4S,8(R)-8-vinylquinuclidin-2-yl)methanol depend also strongly on the used isomer, similar to the physical properties of (RS)-2-(4-(2-methylpropyl)phenyl)-propanoic acid. The heat of fusion of (R)-(6-methoxyquinolin-4-yl)((2S,4S,8(R)-8-vinylquinuclidin-2-yl)methanol is lower than for (S)-2-(4-(2-methylpropyl) phenyl) propanoic acid solution. In the future this experimental data could be used to estimate the binary interaction parameter necessary for thermodynamic drug loading models.

APPENDIX

Table A1. Water Content (w_2/(g·g^{-1})) in the (2E,6E)-3,7,11-Trimethyldodeca-2,6,10-trien-1-ol-rich phase measured with Karl-Fischer Titration and (2E,6E)-3,7,11-Trimethyldodeca-2,6,10-trien-1-ol content (w_1/(g·g^{-1})) in the Water-Rich Phase Measured with HPLC Method at Different Temperatures (T/K)

T	w_2	$10^5 w_1$
K	g·g^{-1}	g·g^{-1}
288.15	0.01841 ± 0.0005	4.19 ± 0.25
293.15	0.01876 ± 0.0005	2.13 ± 0.13
298.15	0.01888 ± 0.0005	1.29 ± 0.10
303.15	0.01939 ± 0.0005	3.57 ± 0.2
308.15	0.01926 ± 0.0005	2.86 ± 0.2
318.15	0.01732 ± 0.0005	2.44 ± 0.14
323.15	0.02148 ± 0.0005	1.99 ± 0.12

Table A2. Solubility of (S)-2-(4-(2-Methylpropyl)Phenyl)-Propanoic Acid (w_1/(g·g^{-1})) in Water Measured with UV−vis Spectroscopy (SLE) at Different Temperatures (T/K)

T	$10^4 w_1$
K	g·g^{-1}
288.15	0.95 ± 0.03
293.15	1.07 ± 0.03
298.15	1.2 ± 0.03
303.15	1.34 ± 0.04
308.15	1.5 ± 0.04
313.15	1.66 ± 0.05
318.15	2.07 ± 0.05

Table A3. (S)-2-(4-(2-Methylpropyl)Phenyl)Propanoic Acid Concentration (w_1/(g·g^{-1})) in the Water-Rich Phase Obtained by Cloud-Point Measurements (LLE) at Different Temperatures (T/K)

T	$10^4 w_1$
K	g·g^{-1}
321.85	2.522 ± 0.07
328.15	2.742 ± 0.08
332.25	2.979 ± 0.09
337.95	3.433 ± 0.07
345.05	4.006 ± 0.08
349.95	4.578 ± 0.07
354.45	5.149 ± 0.08
358.95	5.721 ± 0.07
363.25	6.289 ± 0.09
366.95	6.863 ± 0.08
370.65	7.435 ± 0.09

Table A4. Water Concentration (w_2/(g·g^{-1})) in the (S)-2-(4-(2-Methylpropyl)Phenyl)Propanoic Acid-Rich Phase Obtained by Karl-Fischer Titration at Different Temperatures (T/K)

T	w_2
K	g·g^{-1}
323.15	0.0343 ± 0.0004
333.25	0.0444 ± 0.0003
343.15	0.0572 ± 0.0003
353.15	0.0691 ± 0.0006
363.35	0.0857 ± 0.0005

Table A5. Solubility of (R)-(6-Methoxyquinolin-4-yl)-((2S,4S,8(R)-8-Vinylquinuclidin-2-yl)Methanol (w_1/(g·g^{-1})) in Water Obtained with UV−vis Spectroscopy at Different Temperatures (T/K)

T	$10^4 w_1$
K	g·g^{-1}
288.15	1.9 ± 0.02
293.15	2.02 ± 0.01
298.15	2.13 ± 0.02
303.15	2.27 ± 0.02
308.15	2.42 ± 0.015
313.15	2.54 ± 0.015

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