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Measurement and prediction of solubilities of active pharmaceutical ingredients

Inga Hahnenkamp, Gitte Graubner, Jürgen Gmehling*

Carl von Ossietzky Universität Oldenburg, Technische Chemie, D-26111 Oldenburg, Germany

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ABSTRACT

Solubilities of 2-acetoxy benzoic acid (aspirin), N-acetyl-p-aminophenol (paracetamol) and 2-(p-isobutylphenyl)propionic acid (ibuprofen) have been measured in various solvents and compared with published and predicted data. For the prediction besides the two group contribution models UNIFAC and modified UNIFAC (Dortmund) the quantum chemical approach COSMO-RS (Ol) was used. Additionally melting temperatures and heats of fusion for 2-acetoxy benzoic acid, N-acetyl-p-aminophenol and 2-(p-isobutylphenyl)propionic acid required for the calculations have been determined by differential scanning calorimetry.

1. Introduction

Solution crystallization is an important separation and purification technique, especially in the pharmaceutical industry. For the selection of the most suitable solvent and the design of crystallization processes reliable solubility data for new active pharmaceutical ingredients (API) synthesized are essential. For the selection of the best suited solvent or solvent mixture of a new active compound up till now the measurement of the solubilities of the active pharmaceutical ingredients in different solvents or solvent mixtures is the first step in the development of solution crystallization processes. These measurements are very time-consuming (Sapoundjiev et al., 2005) and require a certain amount of the compound, which is not always available. Therefore a predictive method would be most desirable. The solubility can be calculated using thermodynamic relations taking into account the real behavior. For the development of a reliable predictive method a comprehensive data base with solubilities and pure component data (melting temperature, heat of fusion) is required. For active pharmaceutical ingredients often the pure component data have not been published.

The classical solubility measurement techniques can be roughly divided into isothermal, nonisothermal und polythermal methods. The measurement techniques are explained in detail elsewhere (Mohan et al., 2002). In this work, solid–liquid equilibria of 2-acetoxy benzoic acid (aspirin), N-acetyl-p-aminophenol (paracetamol) and 2-(p-isobutylphenyl)propionic acid (ibuprofen) in various solvents were measured either visually using the polythermal synthetic method (Jakob et al., 1995) or the isothermal gravimetric method (Manifar and Rohani, 2005). The chemical structures of the three active pharmaceutical ingredients investigated in this work are shown in Fig. 1.

The prediction of the solubility of active pharmaceutical ingredients in various solvents has received little attention during the last decades, although technologies as combinatorial chemistry have changed the drug development process substantially. Using these methods hundreds of thousands of new, diverse compounds can be synthesized per year (Glomme et al., 2005). For the purification step the knowledge of the solubility in the various solvents would be desirable.

In this work solubility predictions were carried out using the group contribution methods UNIFAC developed by Fredenslund et al. (1975, 1977) and further developed by Hansen et al. (1991) and modified UNIFAC (Dortmund) developed by Weidlich and Gmehling (1987) and further developed by Gmehling et al. (1993, 1998, 2002). Furthermore the quantum chemical prediction model COSMO-RS (Ol) developed by Grensemann and Gmehling (2005) was applied to predict the solubility of active pharmaceutical ingredients in different solvents.

For this purpose the Dortmund Data Bank (DDBST, 2008) for solid–liquid equilibria, as well as the stored pure component properties of the active pharmaceutical ingredients will be used. At the moment the Dortmund Data Bank contains more than 10,000 solubility data for active pharmaceutical ingredients and most of

* Corresponding author. Tel.: +49 441 798 3831; fax: +49 441 798 3330.
E-mail address: gmehling@tech.chem.uni-oldenburg.de (J. Gmehling).
URL: http://www.uni-oldenburg.de/tchemie (J. Gmehling).

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Nomenclature

f_i	fugacity of component i (kPa)
f_i^0	standard fugacity of component i (kPa)
γ_i	activity coefficient of component i
x_i	mole fraction of component i
Δh	molar enthalpy difference ($J\,mol^{-1}$)
c_p	molar heat capacity ($J\,mol^{-1}\,K^{-1}$)
T	absolute temperature (K)
R	general gas constant ($J\,mol^{-1}\,K^{-1}$)
μ_i	chemical potential of component i in the mixture ($J\,mol^{-1}$)
μ_i^0	chemical potential of the pure substance ($J\,mol^{-1}$)
$\dot{Q}$	heat flow
n	number of moles

Subscripts

m	property at the melting point
tr	property at the triple point
i	type of component

Superscripts

L	liquid phase
S	solid phase
C	combinatorial part
R	residual part

the required pure component data including the structures and σ-profiles for COSMO-RS (Ol).

2. Thermodynamics

Identical to other phase equilibria, the required thermodynamic relations for solid–liquid equilibrium can be derived starting from the isofugacity criterion (Gmehling and Kolbe, 1992):

$$f_i^S = f_i^L \tag{1}$$

Since the fugacity can be described with the help of the activity coefficient and the standard fugacity, the following expressions for the solid and the liquid phase are obtained:

$$f_i^S = x_i^S \gamma_i^S f_i^{0S} \tag{2}$$

$$f_i^L = x_i^L \gamma_i^L f_i^{0L} \tag{3}$$

Using Eq. (1), the solubility of the solute i in the liquid phase can be calculated by:

$$x_i^L = \frac{x_i^S \gamma_i^S f_i^{0S}}{\gamma_i^L f_i^{0L}} \tag{4}$$

For eutectic systems, i.e. for systems which do not form mixed crystals, relation (4) can be simplified. Then for the crystallizing compound one obtains:

$$x_i^L \gamma_i^L = \frac{f_i^{0S}}{f_i^{0L}} \tag{5}$$

An expression for the ratio of the standard fugacities can be obtained via a thermodynamic cycle (Gmehling and Kolbe, 1992). By neglecting the temperature-dependence of the heat capacity difference ($\Delta c_{p,i} = c_{p,i}^L - c_{p,i}^S$), the following equation is obtained:

$$\ln\frac{f_i^{0L}}{f_i^{0S}} = \frac{\Delta h_{m,T_{tr,i}}}{RT}\left(1 - \frac{T}{T_{tr,i}}\right) - \frac{\Delta c_{p,i}\left(T_{tr,i} - T\right)}{RT} + \frac{\Delta c_{p,i}}{R}\ln\frac{T_{tr,i}}{T} \tag{6}$$

This equation can be further simplified. For example the triple point temperatures $T_{tr,i}$ generally differ only very little from the tabulated melting points $T_{m,i}$ ($T_{tr,i} \approx T_{m,i}$). The same is true for the enthalpies of melting at the triple point and the melting point ($\Delta h_{m,T_{tr,i}} \approx \Delta h_{m,T_{m,i}}$). Furthermore the last two terms in Eq. (6) tend to cancel each other at temperatures not far away from the melting point because of their opposite signs. Therefore a simplified equation is obtained to describe the ratio of the standard fugacities.

$$\ln\frac{f_i^{0L}}{f_i^{0S}} = \frac{\Delta h_{m,T_{m,i}}}{RT}\left(1 - \frac{T}{T_{m,i}}\right) \tag{7}$$

This means for the solubility x_i^L of a solute in a solvent or solvent mixture the following equation is obtained:

$$x_i^L = \frac{1}{\gamma_i^L}\exp\left[-\frac{\Delta h_{m,T_{m,i}}}{RT}\left(1 - \frac{T}{T_{m,i}}\right)\right] \tag{8}$$

For the determination of the solubility besides the melting point $T_{m,i}$ and the heat of fusion $\Delta h_{m,i}$ only the activity coefficient of component i is required. While the pure component data can directly be read from the Dortmund Data Bank (DDBST, 2008), which presents the greatest factual data bank for pure component and mixture properties, the activity coefficient γ_i can be calculated with predictive models, such as e.g. UNIFAC, modified UNIFAC (Dortmund) and COSMO-RS (Ol).

3. Material and purities

The purities of the components used and their suppliers are given in Table 1. The purities of the solvents were checked by gas chromatography and the water concentration (always <300 ppm) was determined by Karl Fischer titration.

4. Experimental section

4.1. Solid–liquid equilibria

There is a significant lack of published solubility data of adequate quality with regard to active pharmaceutical ingredients and especially for new drugs. Therefore solid–liquid equilibria for several active pharmaceutical ingredients in different solvents were measured by two different methods. On the one hand the measurements were carried out by using the synthetic method,

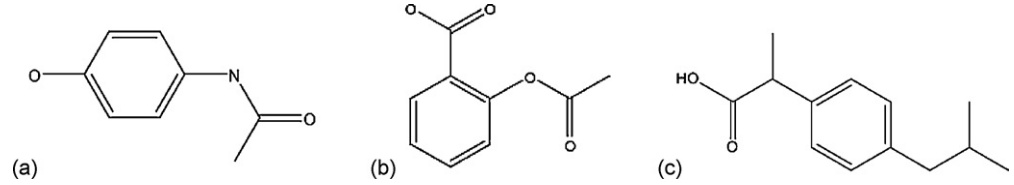

Fig. 1. Structure of (a) paracetamol, (b) aspirin and (c) ibuprofen.

Table 1
Supplier and purity of the chemicals used.

Component	Supplier	Purity (%)
Aspirin	Fluka	>99
Paracetamol	Fluka	>98
Ibuprofen	TCI Europe I0415	>98
Ethanol	VWR	99.8
Acetone	Riedel-de Haën	99.8
2-Propanol	Acros Organics	99.7
Acetonitrile	BDH Prolabo VWR	>99.9
2-Butanone	Acros Organics	>99.9
4-Methyl-2-pentanone	Merck	>99.9
Isopropyl acetate	Acros Organics	>99.9
Heptane	Baker Analyzed	>99.9
3-Methyl-2-butanone	Merck	99.8

in which the melting process is observed visually and the temperature determined at which for a given composition the solid phase just disappears. The equipment consists of a three jacket vessel into which the thermostated equilibrium cell (volume of 160 cm^3) is inserted. Measurements are possible between 185.15 K and 373.15 K. The cryostat liquid flows through the central jacket of the vessel and transfers the heat to the equilibrium cell via a contact medium. The measurements are performed under dry nitrogen to avoid the entry of humidity at low temperature. The temperature is measured by using a platinum resistance thermometer (Model 162 CE, Rosemount) with a precision of ±0.005 K. The conversion and display of the measured resistance is performed by a Metrodology thermometer (Model 1506) manufactured by Hart Scientific. The degree of accuracy of the temperature using the visual method was determined to be 0.015 K. The experimental setup used is shown schematically in Fig. 2. A detailed description of the measurement procedure is available (Jakob et al., 1995).

On the other hand the solubility was determined with the analytical gravimetric method. The equipment consists of a shaker with an aluminum heating block, into which 20 mL vials are inserted. These vials are captured with a septum, a Teflon panel and a cap, so that the components cannot evaporate. The heating block allows measurements between 293.15 K and 473.15 K. The temperature is measured using a platinum resistance thermometer (Model T5, Conatex). The conversion and display of the measured resistance is performed by a Metrodology thermometer (Model 1502A, Hart Scientific). The precision of the used thermometer is ±0.006 K. For the measurement the active pharmaceutical ingredient is added to the solvent in a 20 mL vial in excess and the resulting suspension is shaken at the desired temperature for a sufficient time to reach phase equilibrium. The objective is to form a saturated solution, as indicated by observation of a surplus of unsolved active pharmaceutical ingredient. Afterwards the surplus solute is allowed to settle down, before 5 mL of the clear sample is transferred to weighed glass vials. The weight of the saturated clear solution and of the final dry residue after solvent evaporation is recorded with a Sartorius balance (model CP225D) with an accuracy of ±0.01 mg after complete dryness was achieved.

4.2. Pure component properties

A "heat flux" differential scanning calorimeter from TA Instruments (model DSC Q100) was used to determine the fusion data (melting temperature, heat of fusion) of several components. Differential scanning calorimetry is a technique which detects temperature and heat flows caused by changes in heat capacity or by endothermic or exothermic processes, e.g. phase changes of materials as a function of time and temperature. The basic principle of a DSC equipment and the measurement procedure is described in literature (Höhne et al., 1996; Diedrichs and Gmehling, 2006). The instrument used allows measurements between 93 K and 823 K, because the DSC is equipped with a liquid nitrogen cooling system. The hermetic sample pan, which consists of aluminum and which has an internal volume of 40 μL, withstands an internal pressure up to 3 bar. The sample mass is in the range of 5–15 mg. To prepare the samples a Sartorius balance (model CP225D) with an accuracy of ±0.01 mg has been used.

5. Prediction section

Reliable knowledge of the phase equilibrium behavior of the system to be separated is necessary for the design, development and optimization of separation processes. If the required experimental data are not available, prediction methods can be applied for process development. In this work the solid–liquid equilibria of the investigated binary pharmaceutical-solvent mixtures were predicted by the two group contribution methods UNIFAC and modified UNIFAC (Dortmund) and the quantum chemical method COSMO-RS (Ol) assuming eutectic behavior.

5.1. Prediction using group contribution models

These methods are based on the group contribution concept, which assumes that a mixture does not consist of molecules but of functional groups. The advantage is that the required activity coefficient γ_i can be predicted on the basis of interactions between the limited numbers of functional groups. In this paper the group

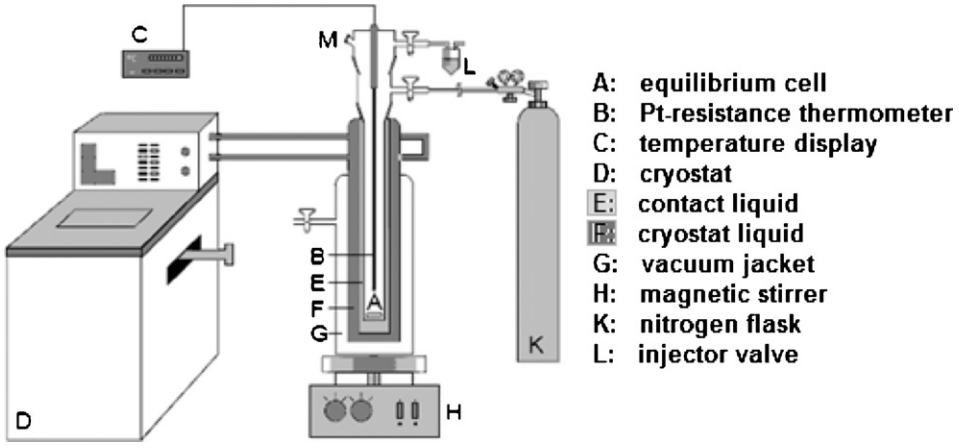

Fig. 2. Static apparatus for SLE measurements.

contribution method UNIFAC (UNIQUAC Functional Group Activity Coefficients) published by Fredenslund et al. (1975, 1977) and further developed by Hansen et al. (1991) and its improved version modified UNIFAC (Dortmund) developed by Weidlich and Gmehling (1987) and further developed by Gmehling et al. (1993, 1998, 2002) were used to predict the required activity coefficients. In both group contribution methods the activity coefficient is calculated by two contributions:

$$\ln \gamma_i = \ln \gamma_i^C + \ln \gamma_i^R \quad (9)$$

The combinatorial part (C) is temperature-independent and represents the contribution of the excess entropy, which takes into account the different size and shape of the molecules. This part can be calculated using van der Waals volumes R_k and surface areas Q_k of the functional groups. The residual part (R) takes into account the attractive forces between the molecules.

The main changes in modified UNIFAC (Dortmund) contain firstly a somewhat different calculation of the combinatorial part, in order to describe systems with molecules very different in size. Furthermore in contrast to original UNIFAC temperature dependent group interaction parameters are used, which are fitted simultaneously to a comprehensive data base (UNIFAC Consortium, 2008).

5.2. Prediction using a quantum chemical method

The COSMO-RS (Ol) model (conductor-like screening model for real solvents), developed by Grensemann and Gmehling (2005), is a modification of the COSMO-RS model of Klamt (2005). It uses quantum chemical methods in combination with approaches of statistical thermodynamics, to predict the chemical potential of a component based on its structure. This method is based on the concept, that the solvent is considered as a dielectric continuum, in which the solvate molecule is bedded. The electrostatic interaction between the solvate molecule and the continuum is described by screening charges on a contact surface. This surface is basically identical to the van der Waals-surface of the solvate molecule. The activity coefficient is calculated as follows:

$$\gamma_i = \exp\left(\frac{\mu_i - \mu_i^0}{RT}\right) \quad (10)$$

whereas μ_i^0 stands for the chemical potential of the pure substance and μ_i for the chemical potential of the component in the mixture.

6. Results and discussion

Solid–liquid equilibrium data for paracetamol, aspirin and ibuprofen in several solvents were measured. The experimental solubilities using the synthetic method for paracetamol with ethanol, acetone, water and 2-propanol and aspirin with ethanol, acetone, 2-butanone, 4-methyl-2-pentanone and isopropyl acetate as well as ibuprofen with acetonitrile, 2-butanone, heptane, 2-propanol, isopropyl acetate and 3-methyl-2-butanone are given in Table 2

.

The experimental solubilities of paracetamol in ethanol and acetone measured additionally with the gravimetric method are listed in Table 3.

The data for the pure substances required for the solid–liquid equilibrium calculations are listed in Table 4. The fusion data for paracetamol, aspirin and ibuprofen were measured with the DSC Q100 from TA Instruments with an accuracy of ±2%, the other data were taken from the Dortmund Data Bank (DDBST, 2008).

Figs. 3 and 4 show the predicted results using UNIFAC, modified UNIFAC (Dortmund) and COSMO-RS (Ol) together with the experimental and the published solubility data as function of temperature for the systems paracetamol/ethanol, paracetamol/acetone, parac-

Table 2
Solid–liquid equilibrium data for paracetamol, aspirin and ibuprofen in several solvents measured with the synthetic method.

x_1	T (K)
Paracetamol (1)–ethanol (2)	
0.0304	258.97
0.0402	277.34
0.0600	295.03
0.0806	309.96
0.1004	321.03
Paracetamol (1)–acetone (2)	
0.0202	271.12
0.0401	302.54
0.0601	318.84
Paracetamol (1)–water (2)	
0.00102	280.92
0.00200	302.26
0.00389	321.83
Paracetamol (1)–2-propanol (2)	
0.0240	269.50
0.0360	289.37
0.0520	305.04
Aspirin (1)–ethanol (2)	
0.0198	269.25
0.0399	286.99
0.0599	298.29
0.0798	306.82
0.1002	313.58
0.1498	323.16
Aspirin (1)–acetone (2)	
0.0205	246.44
0.0504	275.37
0.0699	289.26
0.0991	304.25
0.1307	317.57
Aspirin (1)–2-butanone (2)	
0.0370	273.36
0.0521	287.04
0.0700	299.01
0.0800	304.77
0.0897	309.71
Aspirin (1)–4-methyl-2-pentanone (2)	
0.0200	274.87
0.0299	289.39
0.0499	307.62
Aspirin (1)–isopropyl acetate (2)	
0.0205	286.69
0.0278	295.43
0.0378	307.26
0.0429	311.13
Ibuprofen (1)–acetonitrile (2)	
0.0149	280.08
0.0199	284.58
0.0402	295.68
0.0588	301.82
0.0691	304.00
0.0794	306.21
Ibuprofen (1)–2-butanone (2)	
0.1033	271.02
0.1212	275.96
0.1403	280.37
0.1598	284.51
0.1802	288.42
Ibuprofen (1)–heptane (2)	
0.0100	281.91
0.0200	290.56
0.0299	295.56
0.0399	299.21
0.0500	302.07

Table 2 (*Continued*)

x_1	T (K)
Ibuprofen (1)–2-propanol (2)	
0.0948	278.08
0.1298	283.54
0.1400	285.78
Ibuprofen (1)–isopropyl acetate (2)	
0.1000	276.33
0.1156	279.83
0.1284	282.49
0.1415	285.12
Ibuprofen (1)–3-methyl-2-butanone	
0.1277	276.79
0.1404	279.80
0.1506	282.72

Table 3
Solid–liquid equilibrium data for paracetamol/ethanol and paracetamol/acetone measured with the gravimetric method.

x_1	T (K)
Paracetamol (1)–ethanol (2)	
0.057	298.15
0.063	302.85
0.079	313.63
Paracetamol (1)–acetone (2)	
0.033	298.15
0.042	302.85
0.050	307.25

Table 4
Thermodynamic pure component data for the substances investigated.

	Formula/CAS-Nr.	$\Delta h_{m,i}$ (J mol^{-1})	$T_{m,i}$ (K)
Paracetamol	$C_8H_9NO_2$/103-90-2	27,405	442.18
Aspirin	$C_9H_8O_4$/50-78-2	32,555	408.95
Ibuprofen	$C_{13}H_{18}O_2$/15687-27-1	26,422	348.25
Ethanol	C_2H_6O/64-17-5	5017.5	158.65
Acetone	C_3H_6O/67-64-1	5687.3	178.35
Water	H_2O/7732-18-5	5996.1	273.15
2-Propanol	C_3H_8O/67-63-0	5369.3	183.65
2-Butanone	C_4H_8O/78-93-3	8433.3	186.48
4-Methyl-2-pentanone	$C_6H_{12}O$/108-10-1	11,979	193.83
Isopropyl acetate	$C_5H_{10}O_2$/108-21-4	8873.8	199.75
Acetonitrile	C_2H_3N/75-05-8	8904.0	229.30
Heptane	C_7H_{16}/142-82-5	14,152	182.55
3-Methyl-2-butanone	$C_5H_{10}O$/563-80-4	9336.6	181.00

etamol/water, aspirin/ethanol and aspirin/acetone. The results of the solubility measured with the synthetic method are in good agreement with the data reported in literature, whereas the solubilities determined gravimetrically are a little smaller than the published and the new experimental data. Due to the easier and faster measurements by the synthetic method and its more precise results most solid–liquid equilibria were measured using the visual method.

Figs. 5–7 show the experimental solubility data measured with the visual synthetic method and the predicted results using UNIFAC, modified UNIFAC (Dortmund) and COSMO-RS (Ol) for paracetamol, aspirin and ibuprofen in different solvents.

Obviously the predicted solubilities of the active pharmaceutical ingredients using the group contribution models UNIFAC and modified UNIFAC (Dortmund) tend to systematically underestimate the

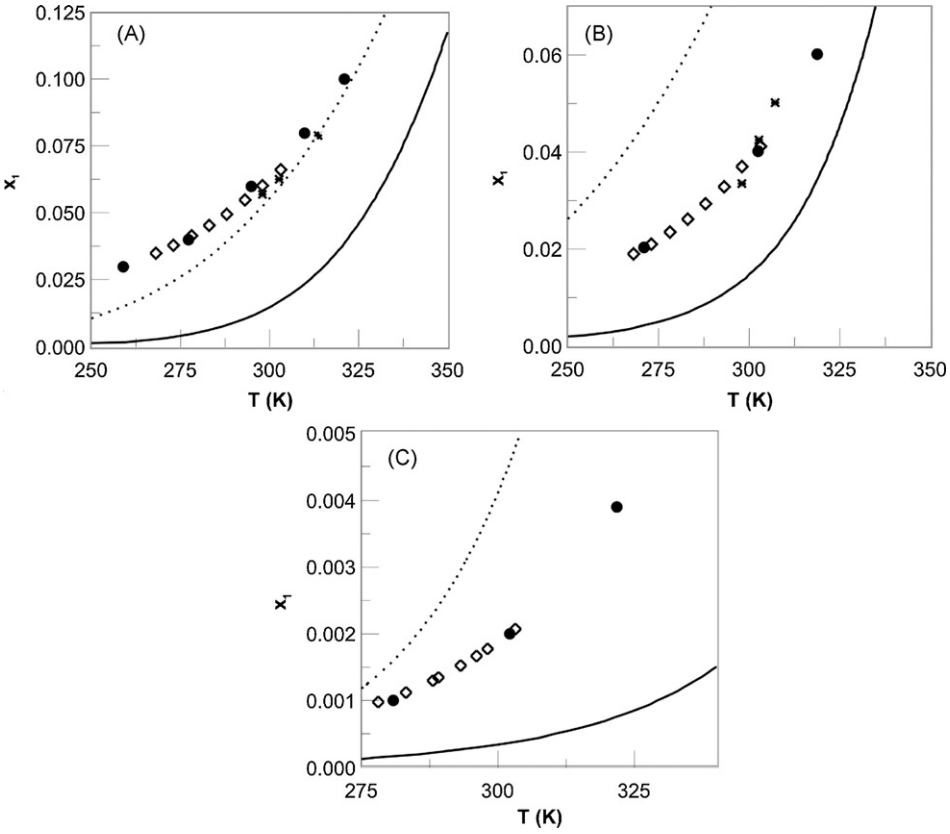

Fig. 3. Experimental, published and predicted solid–liquid equilibrium data for the systems studied. (a) paracetamol (1)–ethanol (2), (b) paracetamol (1)–acetone (2), (c) paracetamol (1)–water (2), (●) experimental data (synthetic method), (✱) experimental data (gravimetric method), (◊) experimental data from Granberg and Rasmuson (1999), (—) modified UNIFAC (Dortmund), (···) COSMO-RS (Ol).

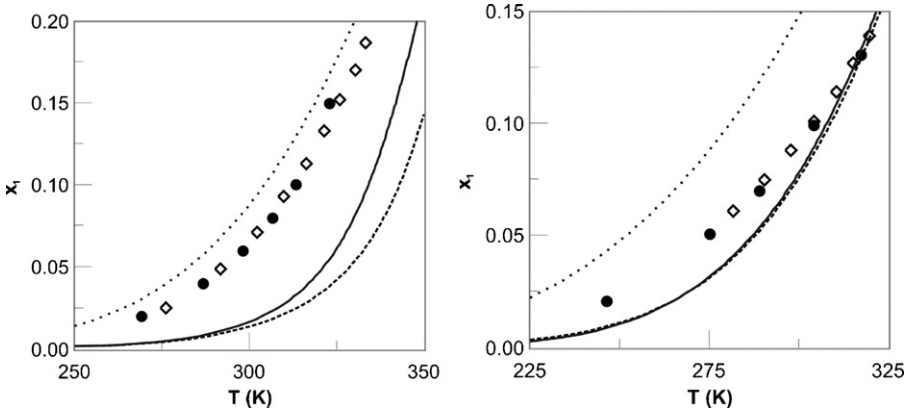

Fig. 4. Experimental, published and predicted solid–liquid equilibrium data for the systems studied. (a) aspirin (1)–ethanol (2), (b) aspirin (1)–acetone (2), (●) experimental data (synthetic method), (◊) experimental data from (a) Frank et al. (1999) and (b) Perlovich and Bauer-Brandl (2003), (—) modified UNIFAC (Dortmund), (- - -) UNIFAC, (···) COSMO-RS (Ol).

Table 5
Comparison of the results of the group contribution methods UNIFAC, modified UNIFAC (Dortmund) and the quantum chemical model COSMO-RS (Ol) for the absolute temperature *T*.

System	UNIFAC		Modified UNIFAC (Do)		COSMO-RS (Ol)	
	MAD (K)	RMSDr (%)	MAD (K)	RMSDr (%)	MAD (K)	RMSDr (%)
Aspirin/ethanol	33.22	11.39	25.57	8.99	9.25	3.25
Aspirin/acetone	8.77	4.14	8.35	4.04	23.83	8.42
Aspirin/2-butanone	26.79	9.42	25.41	8.99	2.46	1.17
Aspirin/4-methyl-2-pentanone	24.15	8.57	24.92	8.90	3.11	1.26
Aspirin/isopropyl acetate	23.45	7.97	20.50	6.97	13.05	4.37
Ibuprofen/acetonitrile	9.36	3.33	5.28	1.79	24.42	8.35
Ibuprofen/2-butanone	2.56	0.92	4.61	1.72	19.76	7.10
Ibuprofen/heptane	9.86	3.53	2.36	1.01	11.18	3.82
Ibuprofen/2-propanol	7.68	2.72	15.22	5.39	10.45	3.75
Ibuprofen/isopropyl acetate	1.43	0.51	7.16	2.56	18.19	6.49
Ibuprofen/3-methyl-2-butanone	2.31	0.83	4.63	1.68	18.99	6.79
Average	13.60	4.85	13.09	4.73	14.06	4.98

solubility, contrary to the quantum chemical model COSMO-RS (Ol), which has the tendency to overestimate the solubility of the investigated active pharmaceutical ingredients.

Tables 5 and 6 summarize the mean absolute (MAD) and the relative root mean square deviations (RMSDr) for eleven solid–liquid equilibria measured, containing ibuprofen or aspirin in several solvents.[1] All the predictions were carried out using the group contribution methods UNIFAC and modified UNIFAC (Dortmund) and the quantum chemical method COSMO-RS (Ol). The relative root mean square deviation in the temperature refers to the calculation of the liquidus line of the mixture for the measured mole fractions and the relative root mean square deviation in the mole fraction refers to the calculation of the mole fraction for the given temperature. Both relative deviations were calculated using the following equation:

$$\mathrm{RMSDr}\,(\%) = 100\sqrt{\frac{1}{n}\sum_{i}\left(\frac{X_{i,\mathrm{exp}} - X_{i,\mathrm{calc}}}{X_{i,\mathrm{exp}}}\right)^2} \tag{11}$$

where n is the number of data points and X is the absolute temperature T or the mole fraction x_i.

It appears that all three models deliver nearly the same root mean square deviation for the temperature from 4.73% to 4.98%. Whereas the model modified UNIFAC (Dortmund) provides the lowest deviation, the second best description is achieved by the UNIFAC model with a deviation of 4.85%. With a root mean square deviation of 4.98% in the temperature, the model COSMO-RS (Ol)

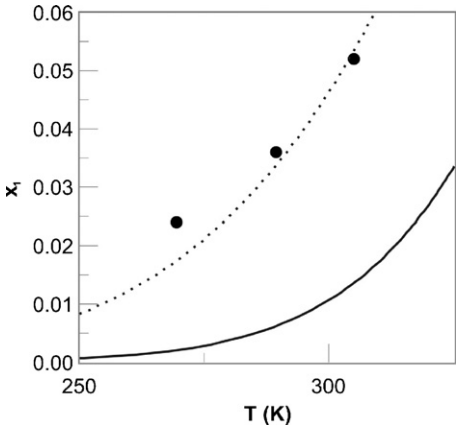

Fig. 5. Experimental and predicted solid–liquid equilibrium data for the system paracetamol (1)–2-propanol (2), (●) experimental data (synthetic method), (—) modified UNIFAC (Dortmund), (···) COSMO-RS (Ol).

[1] Please note, that the UNIFAC model could not be applied for paracetamol, due to a missing structural group, so systems containing this solute are not included in the comparison.

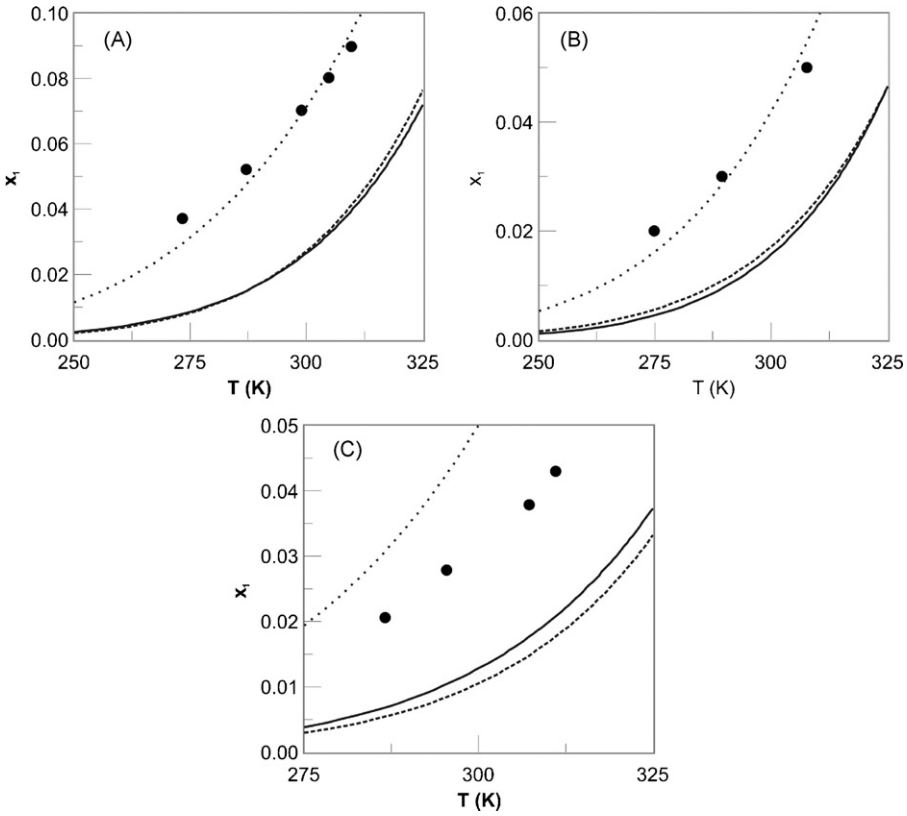

Fig. 6. Experimental and predicted solid–liquid equilibrium data for the systems (a) aspirin (1)–2-butanone (2), (b) aspirin (1)–4-methyl-2-pentanone (2), (c) aspirin (1)–isopropyl acetate (2), (●) experimental data (synthetic method), (—) modified UNIFAC (Dortmund), (- - -) UNIFAC, (···) COSMO-RS (Ol).

Table 6
Comparison of the results of the group contribution methods UNIFAC, modified UNIFAC (Dortmund) and the quantum chemical model COSMO-RS (Ol) for the mole fraction x_i.

System	UNIFAC		Modified UNIFAC (Do)		COSMO-RS (Ol)	
	MAD (mol%)	RMSDr (%)	MAD (mol%)	RMSDr (%)	MAD (mol%)	RMSDr (%)
Aspirin/ethanol	6.66	90.44	6.40	87.95	2.38	34.76
Aspirin/acetone	4.47	69.58	4.32	68.33	0.61	18.31
Aspirin/2-butanone	4.18	66.48	4.12	65.99	0.39	10.28
Aspirin/4-methyl-2-pentanone	2.00	63.68	2.13	68.04	0.33	12.85
Aspirin/isopropyl acetate	2.07	66.14	1.84	59.01	2.03	61.12
Ibuprofen/acetonitrile	2.67	67.72	2.17	43.80	11.75	273.64
Ibuprofen/2-butanone	1.24	8.76	2.29	17.83	8.43	62.31
Ibuprofen/heptane	2.02	85.04	0.35	18.19	1.81	60.09
Ibuprofen/2-propanol	3.70	30.32	6.45	52.91	5.05	44.03
Ibuprofen/isopropyl acetate	0.75	6.13	3.36	27.92	8.00	67.20
Ibuprofen/3-methyl-2-butanone	1.06	7.62	2.33	17.09	8.02	57.62
Average	2.80	51.08	3.25	47.91	4.44	63.84

performs a little worse, when compared to the two group contribution methods.

With a relative root mean square deviation of 47.91% in the liquid phase composition modified UNIFAC (Dortmund) delivers the lowest deviations. The second best description is achieved by UNIFAC (RMSDr = 51.08%). The COSMO-RS (Ol) provides the highest deviation of 63.84%. Obviously both group contribution models deliver better results for ibuprofen than for aspirin, contrary to the quantum chemical model COSMO-RS (Ol). In the case of aspirin there are large deviations between the experimental values and those predicted by the group contribution methods, whereas in the case of ibuprofen the highest deviations are observed for the model COSMO-RS (Ol). Not surprising the relative deviation is particular high in solvents in which the solubility of the solute is very low, e.g. ibuprofen in acetonitrile.

Although the mean absolute deviation (MAD) in the mole fraction between the experimental and the predicted values is not very high, the relative root mean square deviation increases. With a mean absolute deviation of 2.80 mol% UNIFAC delivers the lowest deviation, even though it provides the second best description regarding to the relative root mean square deviation (51.08%). The second best results are obtained using modified UNIFAC (Dortmund) (MAD = 3.25 mol%) and the worst results by COSMO-RS (Ol) (MAD = 4.44 mol%).

The next step was to analyze, if the prediction methods are able to determine the most suitable solvent. This means the solvent which shows the highest solubility for the active pharmaceutical ingredients. Therefore for each of the systems with aspirin and ibuprofen the solubilities for a selected temperature (aspirin: 298.15 K and ibuprofen 282 K) was determined. Then it

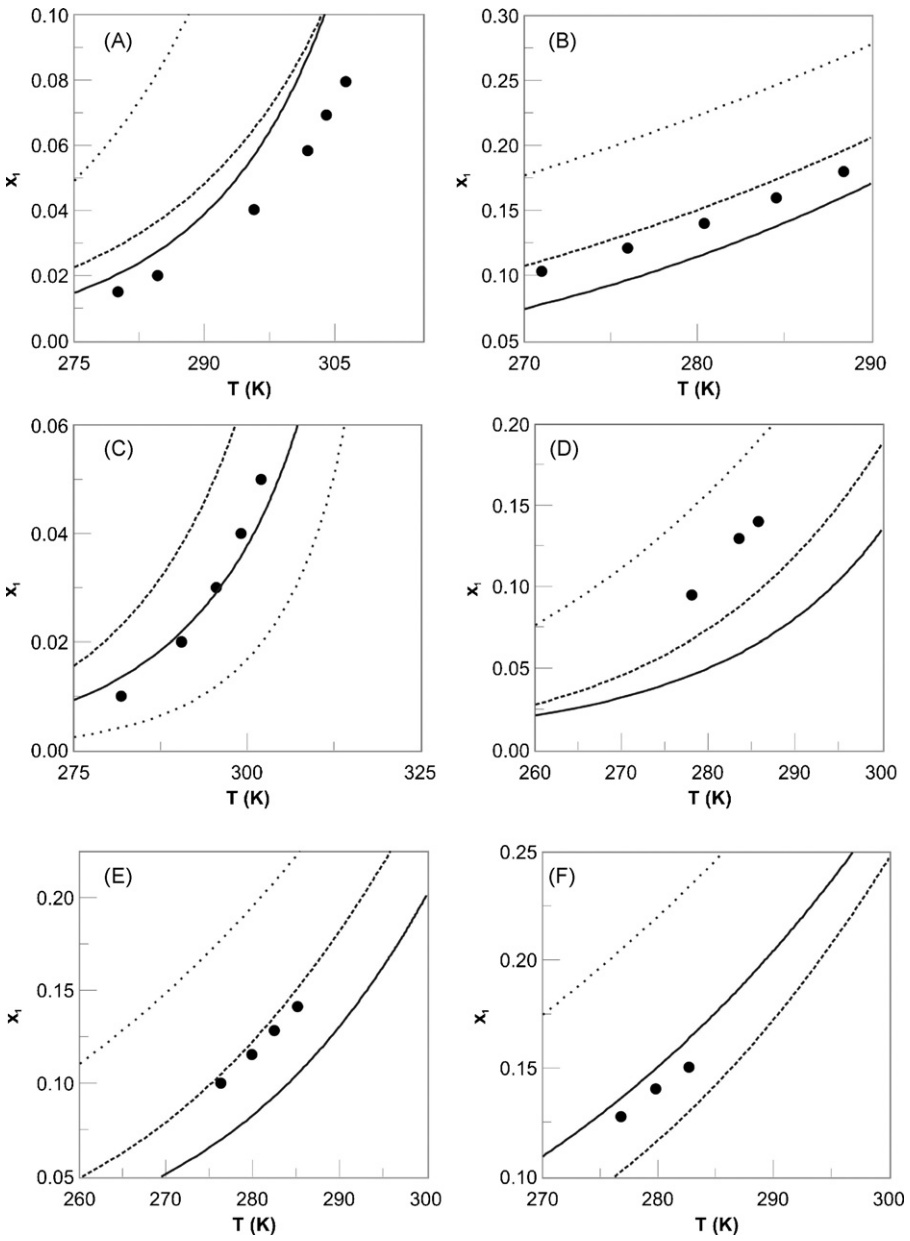

Fig. 7. Experimental and predicted solid–liquid equilibrium data for the systems (a) ibuprofen (1)–acetonitrile (2), (b) ibuprofen (1)–2-butanone (2), (c) ibuprofen (1)–heptane (2), (d) ibuprofen (1)–2-propanol (2), (e) ibuprofen (1)–isopropyl acetate (2), (f) ibuprofen (1)–3-methyl-2-butanone (2), (●) experimental data (synthetic method), (—) modified UNIFAC (Dortmund), (- - -) UNIFAC, (· · ·) COSMO-RS (Ol).

was checked, whether the models are able to find the solvent with the highest solubility. In Tables 7 and 8, the experimental solubilities for aspirin and ibuprofen in the solvents investigated are listed together with the predicted values. The experimental and predicted highest solubilities are always given by bold font. In the case of aspirin all three models are able to predict the best suited solvent (acetone). In the case of ibuprofen modified UNIFAC (Dortmund) identifies the best suited solvent 3-methyl-2-butanone. UNIFAC and COSMO-RS (Ol) detect 2-butanone as the most appropriate solvent and 3-methyl-2-butanone as the secondary best suited one.

Table 7
Experimental solubilities for aspirin (1) in several solvents listed from highest to lowest value and predicted values with the models UNIFAC, modified UNIFAC (Dortmund) and COSMO-RS (Ol) at $T = 298.15$ K.

Solvent (2)	Exp. data x_1	UNIFAC x_1	Modified UNIFAC (Dortmund) x_1	COSMO-RS (Ol) x_1
Acetone	**0.0870**	**0.0319**	**0.0339**	**0.0817**
2-Butanone	0.0685	0.0244	0.0249	0.0674
Ethanol	0.0579	0.0054	0.0065	0.0400
4-Methyl-2-pentanone	0.0386	0.0158	0.0143	0.0393
Isopropyl acetate	0.0300	0.0096	0.0117	0.0468

Table 8
Experimental solubilities for ibuprofen (1) in several solvents listed from highest to lowest value and predicted values with the models UNIFAC, modified UNIFAC (Dortmund) and COSMO-RS (Ol) at $T = 282$ K.

Solvent (2)	Exp. data x_1	UNIFAC x_1	Modified UNIFAC (Dortmund) x_1	COSMO-RS (Ol) x_1
3-Methyl-2-butanone	**0.1483**	0.1606	**0.1267**	0.2307
2-Butanone	0.1475	**0.1608**	0.1247	**0.2335**
Isopropyl acetate	0.1260	0.1337	0.0913	0.2064
2-Propanol	0.1217	0.0818	0.0552	0.1688
Acetonitrile	0.0167	0.0320	0.0231	0.0716
Heptane	0.0101	0.0232	0.0136	0.0042

7. Conclusions

The selection of the best suited solvent is of great importance for the purification of active pharmaceutical ingredients during drug development. The liquidus lines of paracetamol, aspirin and ibuprofen in various solvents were measured either with the synthetic method or gravimetrically. The experimental results are in good agreement with published data.

The experimental solubilities were compared with the predicted results of the group contribution method UNIFAC, modified UNIFAC (Dortmund) and the quantum chemical approach COSMO-RS (Ol). The group contribution model modified UNIFAC (Dortmund) provides the lowest root mean square deviations for the temperature and the solubilities. The second best description is achieved by the UNIFAC model, followed by the quantum chemical method COSMO-RS (Ol). Regarding the determination of the best suited solvent, modified UNIFAC (Dortmund) is able to predict the solvent which shows the highest solubility for the two active pharmaceutical ingredients (aspirin, ibuprofen) investigated.

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