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Solubility and pK_a determination of six structurally related phenothiazines

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ABSTRACT

Solubilities of six structurally related phenothiazines, namely chlorpromazine hydrochloride, fluphenazine dihydrochloride, promazine hydrochloride, thioridazine hydrochloride, trifluoperazine dihydrochloride, and triflupromazine hydrochloride at constant pH were measured in the temperature range from 290 K to 350 K in three important drugs solvents: water, ethanol and 1-octanol using the dynamic method and UV–vis method. Dissociation constants and corresponding pK_a values of drugs were obtained with Bates–Schwarzenbach method at temperature 298.15 K in the buffer solutions. Our experimental pK_a values for chlorpromazine hydrochloride, fluphenazine dihydrochloride, promazine hydrochloride, thioridazine hydrochloride, trifluoperazine dihydrochloride, and triflupromazine hydrochloride are 9.15, 10.01, 9.37, 8.89, 8.97, and 9.03, respectively. The basic thermal properties of pure drugs i.e. melting and solid–solid phase transition as well as glass-transition temperatures, the enthalpy of melting and phase transitions and the molar heat capacity at glass transition (at constant pressure) were measured with differential scanning microcalorimetry (DSC) technique. Molar volumes were calculated with Barton group contribution method. The experimental solubility data were correlated by means of three commonly known G^E equations: the Wilson, NRTL and UNIQUAC with the assumption that the systems studied here have revealed simple eutectic mixtures. The root-mean-square deviations of temperature were used for the precision of the correlation. The activity coefficients of drugs at saturated solutions in each correlated binary mixture were calculated from the experimental data. These new data will help in all prediction-methods and their precision.

1. Introduction

The main objective of the present study was to examine the temperature dependent solubility of six drugs: chlorpromazine hydrochloride (CHLPRO), fluphenazine dihydrochloride (FLPHE), promazine hydrochloride (PRO), thioridazine hydrochloride (THRID), trifluoperazine dihydrochloride (TFLPER), triflupromazine hydrochloride (TFLPRO) at constant, natural pH in water, ethanol and 1-octanol. Another objective is the study of thermophysical properties of chosen drugs, namely the temperature of melting and phase transitions, the enthalpy of melting and phase transitions, which are necessary for the thermodynamic description of solubility. Approaches for modelling the data measured with different correlation G^E models are usually evaluated. The parameters of the correlation models are capable to describe the drug solubility at temperatures other than measured and in ternary systems, for example in the binary solvent mixture. As a result of the correlation, the activity coefficients of drugs in aqueous and alcoholic solutions were achieved. One more objective was the study of the pK_a values, which are useful for physico-chemical measurements, describing the extent of ionization of functional groups with respect to pH. In this work the Bates–Schwarzenbach method is proposed for all compounds (Bates and Gary, 1961) as the continuation of our previous work with many drugs (Domańska et al., 2009, 2010, 2011a, 2011b). In our opinion this method is more exact; it is the spectrophotometric method not using the high dissolution and extrapolation to the pure substance data.

The solubility of drugs is usually measured with different methods: for very low solubility the classical static-saturation shake-flask method at one temperature is commonly used (Baka et al., 2008; Bergström et al., 2004) and for higher solubility the visual, dynamic method, where the solubility as a function of temperature is obtained (Domańska et al., 2009). The positive of the static-saturation shake-flask method is that the pH-dependent sigmoidal solubility profile can be obtained at constant temperature (Bergström et al., 2004; Avdeef et al., 2000).

All drugs studied have a phenothiazine structure with different functional groups. Phenothiazine derivatives (PHTHs) are the constituents of neuroleptics revealing antipsychotic properties (Szydłowska-Czerniak et al., 2001; Madej and Kościelniak, 2008). PHTHs belong to a big group of tricyclic aromatic compounds. They easily react with halide and organic complexes with metals and form well-defined ion-associated complexes (Monzón and Yudi, 2008). PHTHs, due to their pharmacological properties

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Table 1
Investigated compounds: name, abbreviation, structure, and molar mass.

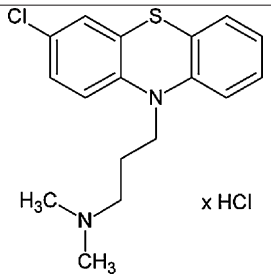
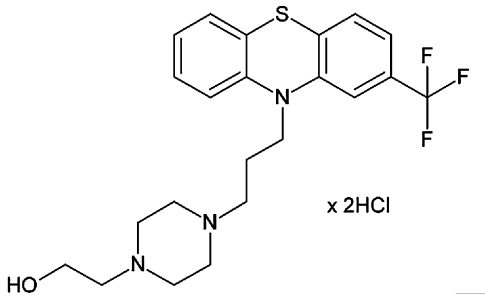
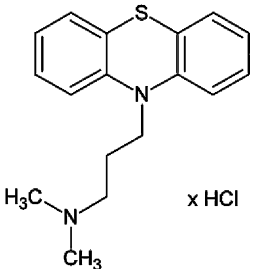
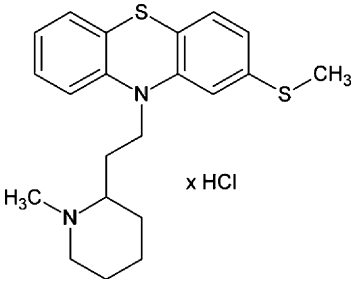
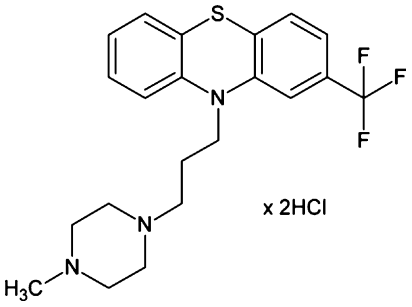
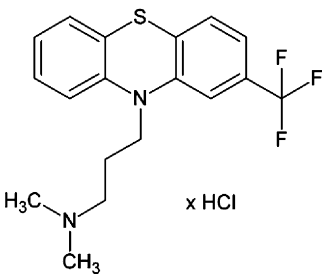
Name of compound	Structural formula	M (g mol^{-1})
Chlorpromazine hydrochloride (CHLPRO)		355.33
Fluphenazine dihydrochloride (FLPHE)		510.50
Promazine hydrochloride (PRO)		320.90
Thioridazine hydrochloride (THRID)		407.40
Trifluoperazine dihydrochloride (TFLPER)		480.43
Triflupromazine hydrochloride (TFLPRO)		388.80

Table 2
Physicochemical characteristics of the drug substances utilized in correlation to the experimental data: temperature and enthalpy of fusion, temperature and enthalpy of solid–solid phase transition, temperature of glass transition, heat capacity changes at glass-transition temperature and molar volumes.

Drug	$T_{fus,1}$ (K)	$\Delta_{fus}H_1$ (kJ mol^{-1})	$T_{tr,1}$ (K)	$\Delta_{tr}H_1$ (kJ mol^{-1})	$T_{g,1}$ (K)	$\Delta Cp_{(g),1}$ (J mol^{-1} K^{-1})	$V_m^{293.15}$ (cm^3 mol^{-1})[a]
Chlorpromazine hydrochloride	471.21	46.90			314.1	139	281.9
Fluphenazine dihydrochloride	538.55	34.46	512.36 488.94	56.2 15.94	291.0	173	352.5
Promazine hydrochloride	454.14	35.01			321.6	292	254.1
Thioridazine hydrochloride	436.62	52.15			350.4	278	310.4
Trifluoperazine dihydrochloride	532.06	19.60	450.07	54.91	314.8	313	343.8
Triflupromazine hydrochloride	518.54	64.54			294.9	139	265.9

[a] Calculated according to the Barton's group contribution method (Barton, 1985).

and potent toxicity, have become group of drugs with increasing interest in clinical study. Halogenation of drugs is commonly used to enhance membrane binding and permeation. Thus in this work the hydrochlorides of PHTHs were investigated. The solubility and pK_a of one drug of this group, the prometazine hydrochloride was already measured in our previous work (Domańska et al., 2009). Three PHTHs were analysed with spectrofluorometric method and the influence of some metal cation on the fluorescence intensity was studied (Szydłowska-Czerniak et al., 2001). The physico-chemical properties and review of analytical methods for identification and determination of PHTHs was presented by Madej and Kościelniak (2008). The pK_a values, and the melting temperature of drugs were presented for 13 PHTHs, but not for hydrochlorides of PHTHs (Madej and Kościelniak, 2008). Thioridazine, the known antidepresant drug was investigated *in vivo* on male Wister rats – the distribution interaction between thioridazine and fluoxetine in the plama and tissues were measured (Wójcikowski and Daniel, 2002). The spectroscopic, electrochemical and the analytical aspect of the mechanism of phenothiazine derivatives oxidation was presented by Karpińska et al. (1996). The kinetics and mechanism of the reaction of PHTHs cation radicals with nucleophiles in aqueous buffer solutions was examined to show more pharmacologically active substances responsible for the binding of PHTHs to receptor proteins (Sackett and McCreery, 1979). The values of pK_a and intrinsic solubilities, S_0 used in this work for PHTHs (CHLPRO, PRO, THRID, TFLPRO) were published many years ago (IJzerman, 1988), however without the information about pH for these values. The interfacial membrane partitioning and permeation of some PHTHs (CHLPRO, PRO, and TFLPRO) were developed and the lipid–water partition coefficients were calculated and measured by the titration calorimetry (Gerebtzoff et al., 2004).

These six drugs selected for the measurements have similar main structure and different functional groups, may interact in different way with water and an alcohol. The effect of pH on the solubility means that the effect of buffer on solubility is well known for the pharmaceutical community (Avdeef, 2007). In this work we did not use buffer solutions; the solubility was measured at natural pH of the drug in the solution.

As a solvent the water, ethanol and 1-octanol were proposed, which are typical media used for delivering of drugs as well as a model compounds of human cell and skin-membrane (1-octanol).

The pK_a values as a useful physico-chemical constant, describing the extent of ionization of functional groups with respect to pH was determined as outlined previously.

2. Materials and methods

Six structurally different phenothiazine derivative drugs were obtained from Sigma Aldrich i.e. chlorpromazine hydrochloride (CAS Registry No. 69-09-0), fluphenazine dihydrochloride (CAS Registry No. 146-56-5), promazine hydrochloride (CAS Registry No. 53-60-1), thioridazine hydrochloride (CAS Registry No. 130-61-0), trifluoperazine dihydrochloride (CAS Registry No. 440-17-5), triflupromazine hydrochloride (CAS Registry No. 1098-60-8). The drugs were used without purification and were used as powder or small crystals. The names, abbreviations, structures and molar masses of the compounds are listed in Table 1.

Water used as a solvent was twice distilled, degassed and filtered with Milipore Elix 3. Other solvents i.e. ethanol and 1-octanol, were also obtained from Sigma Aldrich with a >0.998 mass fraction purity. They were stored under freshly activated molecular sieves of type 4 Å. The buffer solution, containing 0.003981 M borax (CAS Registry No. 1303-96-4; 0.988 mass fraction purity) and 0.007384 M sodium chloride (CAS Registry No. 7647-14-5; 0.999 mass fraction purity), 0.1 M hydrochloric acid (CAS Registry No. 7647-01-0; 0.35 mass fraction purity) and 0.1 M sodium hydroxide solution (CAS Registry No. 1310-73-2; 0.988 mass fraction purity), were prepared from substances delivered by POCH. All solutes were filtrated twice with Schott funnel with 4 μm pores.

The differential scanning microcalorimetry (DSC) technique was used to measure basic thermal properties of the drugs studied i.e. temperatures of fusion ($T_{fus,1}$), temperatures of solid–solid phase transition ($T_{tr,1}$), glass-transition temperatures ($T_{g,1}$), enthalpy of fusion ($\Delta_{fus}H_1$), enthalpy of solid–solid phase transition ($\Delta_{tr}H_1$), and heat capacity change at the glass-transition temperature ($\Delta Cp_{(g),1}$). The applied scan rate was 10 K min^{-1}, with power and recorder sensitivities of 16 mJ s^{-1} and 5 mV, respectively. The apparatus (Thermal Analysis Q200, USA with Liquid Nitrogen Cooling System) was calibrated with a 0.999999 mol fraction purity indium sample. The repeatability of the melting and phase transition temperatures was ±0.1 K (average over three scans). The repeatability of the enthalpy of fusion and phase transitions was ±0.1 kJ mol^{-1} and that of heat capacity at the glass transition temperature was ±3 J mol^{-1} K^{-1}. The thermophysical properties are shown in Table 2. The molar volumes as for the hypothetical subcooled liquid at 298.15 K were calculating using the method of Barton (1985).

A visual-dynamic method of the solubility measurements was used (Domańska, 1986). Mixtures were prepared by weighing pure components within an accuracy of 1×10^{-4} g. Samples were heated slowly (about 5 K h^{-1}) with continuous stirring inside a Pyrex glass cell placed in thermostated water bath. Temperatures of crystal disappearance were measured with an electronic thermometer P 550 (Dostmann Electronic GmbH, Germany), and detected visually. All mixtures were measured by mass, and errors did not exceed 5×10^{-4} in mole fraction. The uncertainties of the temperature measurements were judged to be 0.1 K. The repeatability of the solubility experimental points was ±0.1 K. The results of the solubility measurements are shown in Tables 3–8. Tables include direct experimental results of the solubility equilibrium temperatures, T_{SLE} vs. drug mole fraction, x_1 for the systems {drug (1) + water, or ethanol, or 1-octanol (2)} and activity coefficients at saturated solutions, γ_1, which will be described later.

Table 3
Experimental solubility equilibrium temperatures (T_{SLE}) for {chlorpromazine hydrochloride (1) + solvent (2)} mixtures and activity coefficients γ_1.[a]

x_1	T_{SLE} (K)	γ_1 [a]
Ethanol[b]		
0.0349	294.6	0.04
0.0373	295.7	0.04
0.0382	296.2	0.04
0.0496	301.5	0.04
0.0541	303.3	0.05
0.0600	306.6	0.05
0.0647	307.9	0.05
0.0721	311.5	0.05
0.0835	316.7	0.06
1.0000	471.2	1.00
1-Octanol[b]		
0.0070	299.8	0.15
0.0126	304.8	0.17
0.0156	310.9	0.18
0.0243	319.8	0.20
0.0263	323.1	0.20
0.0326	325.9	0.21
0.0370	333.4	0.22
0.0442	343.4	0.24
1.0000	471.2	1.00

[a] Calculated from the Wilson equation.
[b] The pH of the solution was 7.

Table 5
Experimental solubility equilibrium temperatures (T_{SLE}) for {promazine hydrochloride (1) + water (2)} mixtures and activity coefficients γ_1.[a]

x_1	T_{SLE} (K)	γ_1 [a]
Ethanol[b]		
0.0345	303.2	0.26
0.0426	306.9	0.27
0.0587	313.9	0.28
0.0712	315.6	0.30
0.0786	317.6	0.30
0.0860	319.7	0.31
0.0909	320.5	0.31
0.0948	322.4	0.32
1.0000	454.1	1.00
1-Octanol[b]		
0.0262	310.4	0.44
0.0344	318.8	0.45
0.0441	323.0	0.46
0.0536	326.3	0.47
0.0647	328.7	0.48
0.0771	333.0	0.49
0.0941	337.8	0.51
0.1227	344.2	0.53
0.1772	352.7	0.57
1.0000	454.1	1.00

[a] Calculated from the NRTL equation.
[b] The pH of the solution was 7.

For one system (FLPHE + 1-octanol) the visual method was not applicable because of very low solubility, and the saturation shake-flask method with UV–vis spectroscopy was used. The procedure was described in our previous paper (Domańska et al., 2009). The UV–vis spectrophotometer (Perkin-Elmer Life and Analytical Sciences, Shelton, USA) was used at the temperature range of 293.15–313.15 K.

The pK_a measurements were performed with the Bates–Schwarzenbach method (Bates and Gary, 1961) using a UV-Vis spectrophotometer (Perkin-Elmer Life and Analytical Sciences, Shelton, USA). One buffer was used (mole concentration) i.e. monoethanolamine (0.32000) and hydrochloric acid (0.16000; buffer, pH = 9.2). Buffer was chosen on the basis of the literature of the pK_a of drugs values. Three samples for each drug were prepared: in a buffer solution, a 0.1 M acid solution, and 0.1 M base solution. As references water-buffer, 0.1 M water-acid, and 0.1 M water base solutions were used. Samples were scanned with a

Table 4
Experimental solubility equilibrium temperatures (T_{SLE}) for {fluphenazine dihydrochloride (1) + solvent (2)} mixtures and activity coefficients γ_1.[a]

x_1	T_{SLE} (K)	γ_1 [a]
Ethanol[b]		
0.0008	312.8	0.01
0.0014	320.8	0.01
0.0015	323.3	0.01
0.0018	329.5	0.01
0.0021	330.6	0.01
0.0023	333.0	0.01
1.0000	538.5	1.00
1-Octanol[b]		
0.00005	293.1	0.03
0.00006	298.1	0.03
0.00007	303.1	0.03
0.00009	308.1	0.04
0.00011	313.1	0.04
1.00000	538.5	1.00

[a] Calculated from the NRTL equation for ethanol and UNIQUAC equation for 1-octanol.
[b] The pH of the solution was 7.

Table 6
Experimental solubility equilibrium temperatures (T_{SLE}) for {thioridazine hydrochloride (1) + solvent (2)} mixtures and activity coefficients γ_1.[a]

x_1	T_{SLE} (K)	γ_1 [a]
Water[b]		
0.0029	292.6	0.22
0.0033	293.4	0.21
0.0042	296.0	0.18
0.0050	298.0	0.16
0.0085	301.9	0.11
0.0111	304.5	0.09
0.0156	306.6	0.07
0.0204	307.3	0.06
0.0249	308.3	0.06
0.0303	309.8	0.06
0.0366	310.3	0.06
0.0486	311.2	0.07
1.0000	436.6	1.00
Ethanol[c]		
0.0043	297.6	0.31
0.0052	299.0	0.33
0.0069	302.2	0.35
0.0072	304.2	0.35
0.0089	309.9	0.37
0.0101	312.4	0.39
0.0111	315.9	0.40
1.0000	436.6	1.00
1-Octanol[c]		
0.0025	299.9	0.68
0.0040	310.8	0.69
0.0076	319.2	0.71
0.0101	326.6	0.72
0.0114	328.5	0.72
0.0147	331.5	0.73
0.0176	335.4	0.74
0.0271	343.1	0.75
0.0346	347.9	0.76
0.0451	352.1	0.77
1.0000	436.6	1.00

[a] Calculated from the UNIQUAC equation.
[b] The pH of the solution was 6.
[c] The pH of the solution was 7.

Table 7
Experimental solubility equilibrium temperatures (T_{SLE}) for {trifluoperazine dihydrochloride (1) + solvent (2)} mixtures and activity coefficients γ_1.[a]

x_1	T_{SLE} (K)	γ_1 [a]
Water[b]		
0.0140	299.6	0.01
0.0171	302.3	0.01
0.0228	307.9	0.01
0.0325	313.6	0.01
0.0491	318.0	0.01
1.0000	532.1	1.00
Ethanol[c]		
0.0018	299.8	0.08
0.0023	308.8	0.09
0.0030	312.5	0.09
0.0038	317.1	0.10
0.0049	320.9	0.11
0.0056	322.9	0.11
0.0059	323.5	0.12
0.0063	325.9	0.12
0.0067	328.8	0.12
1.0000	532.1	1.00
1-Octanol[c]		
0.0014	312.6	0.26
0.0017	314.6	0.28
0.0018	319.0	0.28
0.0022	321.4	0.30
0.0031	327.4	0.34
0.0034	331.0	0.35
0.0036	332.0	0.35
0.0035	336.9	0.35
0.0038	339.9	0.36
0.0047	343.4	0.38
0.0066	345.3	0.40
0.0078	347.2	0.41
1.0000	532.1	1.00

[a] Calculated from the NRTL equation for water and ethanol and UNIQUAC equation for 1-octanol.
[b] The pH of the solution was 6.
[c] The pH of the solution was 7.

Table 8
Experimental solubility equilibrium temperatures (T_{SLE}) for {triflupromazine hydrochloride (1) + solvent (2)} mixtures and activity coefficients γ_1.[a]

x_1	T_{SLE} (K)	γ_1 [a]
Water[b]		
0.1118	298.8	0.00
0.1145	300.3	0.00
0.1201	301.4	0.00
0.1291	303.5	0.00
0.1518	311.4	0.00
0.1782	318.7	0.01
0.2144	333.9	0.01
0.2265	340.1	0.01
1.0000	518.5	1.00
Ethanol[c]		
0.0398	292.6	0.00
0.0522	297.9	0.00
0.0599	300.9	0.00
0.0694	305.8	0.01
0.0817	310.4	0.01
0.1053	318.2	0.01
0.1258	330.4	0.02
1.0000	518.5	1.00
1-Octanol[c]		
0.0123	299.8	0.01
0.0152	302.8	0.01
0.0194	310.3	0.01
0.0239	315.0	0.01
0.0291	320.9	0.02
0.0333	323.4	0.02
0.0366	325.9	0.02
0.0407	328.4	0.02
0.0417	329.9	0.02
1.0000	518.5	1.00

[a] Calculated from the Wilson equation for water, UNIQUAC equation for ethanol and NRTL equation for 1-octanol.
[b] The pH of the solution was 6.
[c] The pH of the solution was 7.

scan step of 1 nm from 650 to 190 nm. The following equation was used for the calculations of the pK_a values:

$$pK_a = p(a_H\gamma_{Cl}) - \log\left(\frac{D_{HA} - D}{D - D_{A-}}\right) \quad (1)$$

where pK_a is an acidity constant, $p(a_H\gamma_{Cl})$ is an acidity function, D_{HA}, D_{A-} and D are absorbance values in acid, base and buffer, respectively.

The exact procedure of measurements was described earlier (Domańska et al., 2009). The error of this measurement, calculated with the Gauss method is p$K_a \pm 0.025$.

3. Results and discussion

The DSC measurements show very high temperature of melting of the investigated hydrochlorides from 436.62 K (THRID) to 538.55 K (FLPHE). The enthalpies of fusion for substances without the polymorphism vary from 35.01 kJ mol^{-1} for PRO to 64.54 kJ mol^{-1} for TFLPRO. For two drugs, the very low enthalpy of fusion with decomposition just after the melting temperature was observed and high enthalpy of the solid–solid phase transition at lower than melting temperature. This phenomenon was observed for FLPHE and TFLPER. The FLPHE reveals even two polymorphism forms. The structure of these two compounds is similar. The substituent at nitrogen atom is the same with the only difference of $-CH_2CH_2OH$ group for FLPHE and methyl group (TFLPER). The polymorphism is quite typical for organic compounds and drugs. The glass transition temperatures changed, as for many organic compounds from 291.0 K (FLPHE) to 350.4 K (THRID). The difference in heat capacity changes of glass transition, $\Delta Cp_{(g),1}$ of the measured compounds are presented in Table 2. The values are from 139 J mol^{-1} K^{-1} (CHLPRO and TFLPRO) to 292 J mol^{-1} K^{-1} (PRO).

Solubilities have been determined in three solvents: water, ethanol and 1-octanol for most of the drugs. Medicine expect high solubility of drugs in water, which is comfortable because drugs are well soluble in polar environment of our body. On the other side, drugs revealing high solubility in 1-octanol are well solved in non-polar parts of body as lipids and nervous systems. High solubility in water and alcohols helps drugs to cross the blood–brain barrier. In this work we present the solubility in 15 binary systems. The obtained results are presented in Tables 3–8 and in Figs. 1–6. The information of pH of the saturated solutions is presented in Tables 3–8 together with the experimental data. In general pH = 7 for all systems was observed with exception of solution of THRID, TFLPER and for TFLPRO in water (pH = 6). The spectrophotometric results for FLPHE in ethanol are also included in Table 4. UV–vis spectra for the system with very low solubility is presented in Fig. 7. Unfortunately, it was impossible to measure the solubility of three drugs, namely CHLPRO, FLPHE and PRO in water. The solutions exhibited very high viscosity, without possibility of mixing. These three drugs after the dissolution in water have given gelatine solutions.

Table 9
Values of experimental solubility at pH = 6, extrapolated or interpolated to 298.15 K.

Drug	x_1	c (mol dm^{-3})
Thioridazine hydrochloride	0.0051	0.28
Trifluoperazine dihydrochloride	0.0124	0.70
Triflupromazine hydrochloride	0.1106	6.91

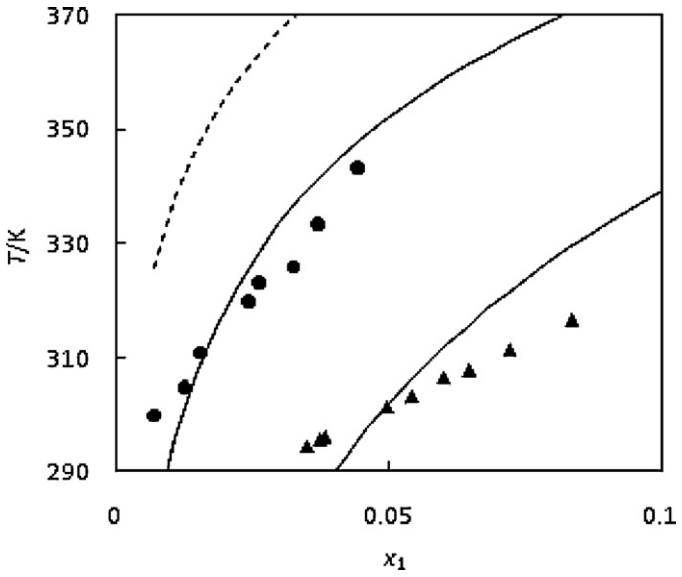


Fig. 1. Experimental and calculated solubility of {chlorpromazine hydrochloride (1) + solvent (2)}: (▲) ethanol and (●) 1-octanol. Solid lines (—) have been designated by the Wilson equation for ethanol and 1-octanol, and the dotted line refers to ideal solubility.

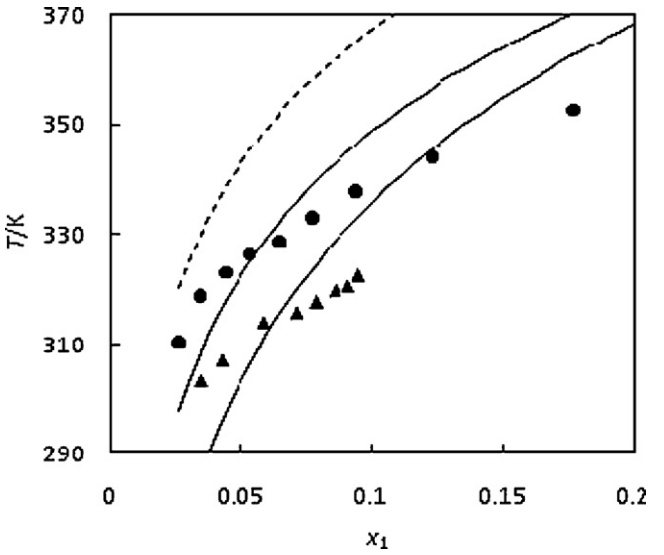


Fig. 3. Experimental and calculated solubility of {promazine hydrochloride (1) + solvent (2)}: (▲) ethanol and (●) 1-octanol. Solid lines (—) have been designated by the NRTL equation for ethanol and 1-octanol, and the dotted line refers to ideal solubility.

On the basis of inspection of Figs. 1–6 the following trends can be noticed: (a) the solubility of all drugs in all solvents was higher than ideal solubility (except of TFLPER in 1-octanol); (b) the solubility of all drugs was higher in water than in 1-octanol; (c) the solubility increases in the order 1-octanol < ethanol < water. These results confirm the idea of using drugs in form of hydrochlorides. In water the dissociation of salts and the hydrogen bonding may play the important role.

From physicochemical point of view, the solubility depends on melting temperature, enthalpy of melting and contamination of polar groups in the molecule. The lower solubility in all solvents was observed for FLPHE with the highest melting temperature, $T_{fus,1}$ = 538.5 K.

The literature data of solubility for the investigated drugs are scarce; the only information is intrinsic solubility equal to 7.2 μmol, 53.5 μmol, 4.9 μmol, and 3.7 μmol, for CHLPRO, PRO, THIRD, and TFLPRO, respectively (IJzerman, 1988). Our values extrapolated, or interpolated to 298.15 K are listed in Table 9. Because of the dissociation of the drugs investigated in water, the values differ from non-dissociated (intrinsic solubility) 2–3 magnitude of order.

The pK_a values are slightly lower or higher (FLPHE, TFLPER) than the literature data previously published (see Table 10). The UV–vis spectra for the systems under study are presented in Figs. 8–13. The ionic strength of solutions used in pK_a constant determination was the same as in the original method presented earlier (Bates and Gary, 1961). New pK_a values were obtained at pH equal to 9.2.

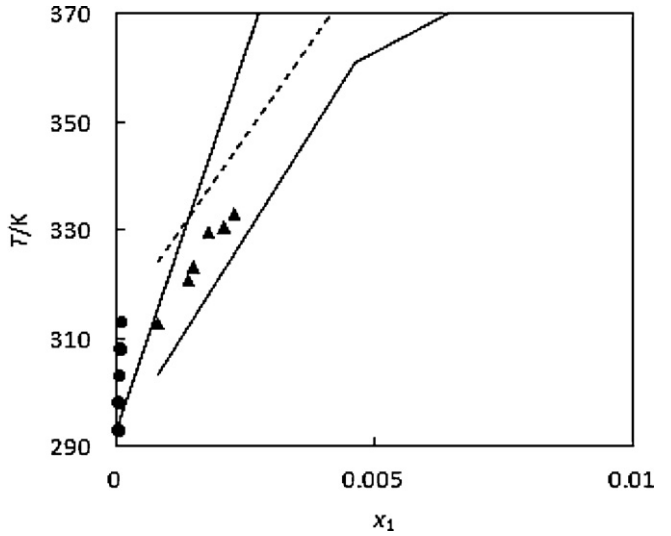


Fig. 2. Experimental and calculated solubility of {fluphenazine dihydrochloride (1) + solvent (2)}: (▲) ethanol and (●) 1-octanol. Solid lines (—) have been designated by the UNIQUAC equation for ethanol and the NRTL equation for 1-octanol, and the dotted line refers to ideal solubility.

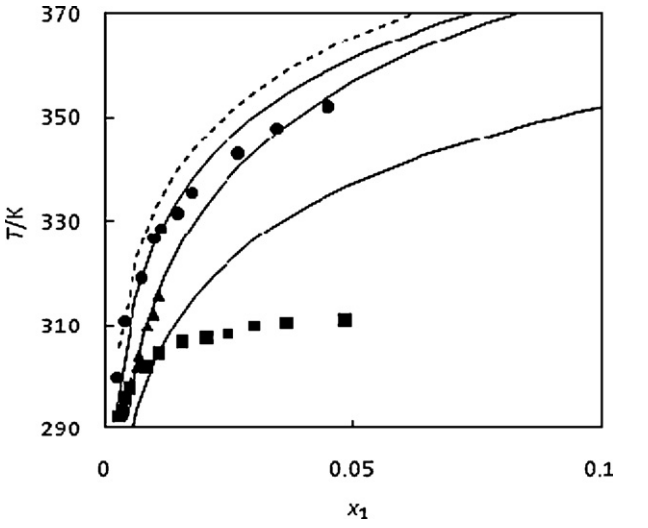


Fig. 4. Experimental and calculated solubility of {thioridazine hydrochloride (1) + solvent (2)}: (■) water, (▲) ethanol and (●) 1-octanol. Solid lines (—) have been designated by the UNIQUAC equation for water, ethanol and 1-octanol, and the dotted line refers to ideal solubility.

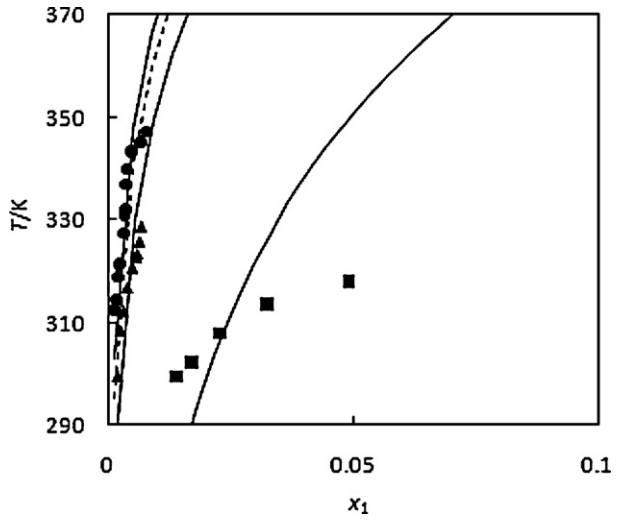


Fig. 5. Experimental and calculated solubility of {trifluoperazine dihydrochloride (1)+solvent (2)}: (■) water, (▲) ethanol and (●) 1-octanol. Solid lines (—) have been designated by the Wilson equation for water, NRTL equation for ethanol and the UNIQUAC equation for 1-octanol, and the dotted line refers to ideal solubility.

4. Modelling

The equation frequently applied to the solid–liquid equilibrium data calculations is (Prausnitz et al., 1986):

$$-\ln x_1 = \frac{\Delta_{fus}H_1}{R}\left(\frac{1}{T}-\frac{1}{T_{fus,1}}\right)+\frac{\Delta_{tr}H_1}{R}\left(\frac{1}{T}-\frac{1}{T_{tr,1}}\right) - \frac{\Delta_{fus}C_{p,1}}{R}\left(\ln\frac{T}{T_{fus,1}}+\frac{T_{fus,1}}{T}-1\right)+\ln\gamma_1 \quad (2)$$

where x_1, γ_1, $\Delta_{fus}H_1$, $\Delta_{fus}C_{p,1}$, $T_{fus,1}$, T, $\Delta_{tr}H_1$ and $T_{tr,1}$ are mole fraction, activity coefficient, enthalpy of fusion, difference in solute heat capacity between the liquid and solid phase at melting temperature, melting temperature, equilibrium temperature, enthalpy of the solid–solid phase transition and transition temperature, respectively. If a solid–solid phase transition occurs before fusion, the solubility equation for temperatures below that of the phase transition must include the effect of the transition. The existence of the solid–solid phase transition for FLPHE (two transitions) and for TFLPER was observed and described in Table 2. The third term with the heat capacity at melting temperature, $\Delta_{fus}C_{p,1}$ is not known, and has to be omitted.

In this study three methods that describe the Gibbs excess free energy of mixing (G^E) the Wilson (Wilson, 1964), NRTL equation (Renon and Prausnitz, 1968) and UNIQUAC equation (Abrams and Prausnitz, 1975) are used to represent the solute activity coefficients, γ_1. Two adjustable parameters of the equations were found by an optimization technique. The objective function was as follows:

$$F(A_1A_2) = \sum_{i=1}^{n} w_i^{-2}[\ln x_{1i}\gamma_{1i}(T_i, x_{1i}, A_1A_2) - \ln a_{1i}]^2 \quad (3)$$

where $\ln a_{1i}$ denotes an "experimental" value of the logarithm of the solute activity, w_i is the weight of an experimental point, A_1 and A_2 are the two adjustable parameters of the correlation equations, i denotes the ith experimental point and n is the number of experimental data. The weights were calculated by means of the

Table 10
Experimental and literature values of pK_a.

Drug	pK_a^{lit}			pK_a^{exp}
Chlorpromazine hydrochloride	9.26[a]	9.40[b]	9.43[c]	9.15
Fluphenazine dihydrochloride	8.1[d]			10.01
Promazine hydrochloride	9.42[e]	9.40[f]	9.42[g]	9.37
Thioridazine hydrochloride	9.16[a]	9.62[b]		8.89
Trifluoperazine dihydrochloride	8.08[h]			8.97
Triflupromazine hydrochloride	9.41[a]	9.29[b]	9.07[i]	9.03

[a] Chatten and Harris (1962).
[b] Vezin and Florence (1979).
[c] Ploemen et al. (2004).
[d] Newton and Kluza (1978).
[e] Seiler (1974).
[f] Madej and Kościelniak (2008).
[g] Karpińska et al. (1996).
[h] Clarke and Cahoon (1987).
[i] Franke et al. (1999).

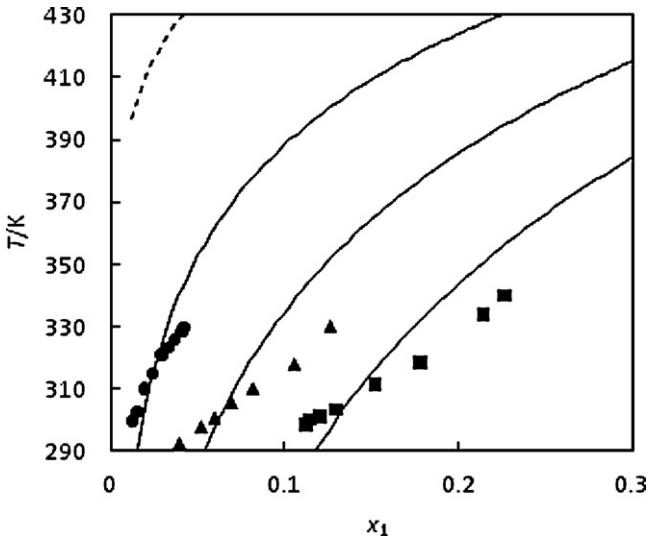


Fig. 6. Experimental and calculated solubility of {trifluprazine hydrochloride (1)+solvent (2)}: (■) water, (▲) ethanol and (●) 1-octanol. Solid lines (—) have been designated by the Wilson equation for water, UNIQUAC equation for ethanol and the NRTL equation for 1-octanol, and the dotted line refers to ideal solubility.

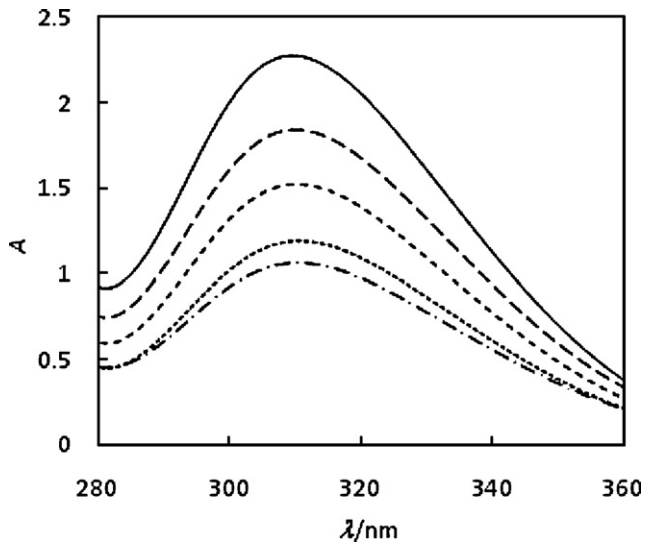


Fig. 7. UV–vis spectra for {fluphenazine dihydrochloride + 1-octanol}: at 293.15 K (–·–); at 298.15 K (···); at 303.15 K (– – –); at 318.15 K (– – –); at 328.15 K (—). λ = 310 nm – wavelength chosen from the calibration curves.

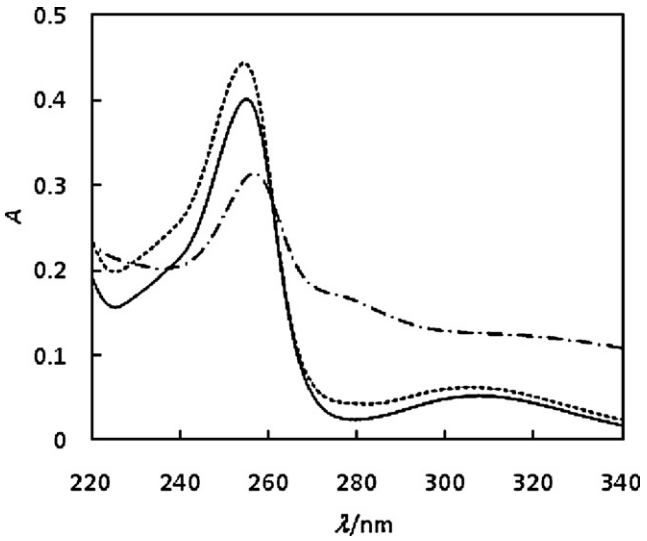


Fig. 8. pK_a measurements (absorbance vs. wavelength): experimental points for {chlorpromazine hydrochloride + water} mixtures: (—) buffer; (···) 0.1 M HCl; (– · –) 0.1 M NaOH.

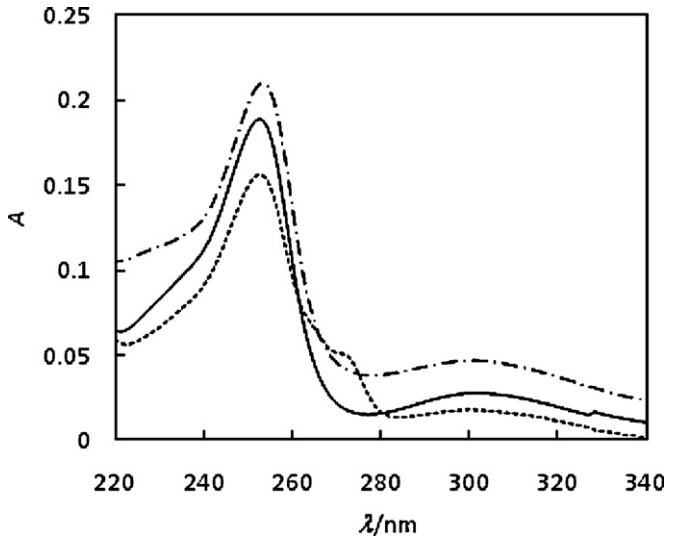


Fig. 10. pK_a measurements (absorbance vs. wavelength): experimental points for {promazine hydrochloride + water} mixtures: (—) buffer; (···) 0.1 M HCl; (– · –) 0.1 M NaOH.

error propagation formula:

$$w_i^2 = \left(\frac{\partial \ln\, x_1\gamma_1 - \partial \ln a_i}{\partial T}\right)^2_{T=T_i} (\Delta T_i)^2 + \left(\frac{\partial \ln x_1\gamma_1}{\partial x_1}\right)^2_{x_1=x_{1i}} (\Delta x_{1i})^2 \quad (4)$$

where ΔT and Δx_1 are the estimated errors in T and x_{1i}, respectively. A_1 and A_2 are model parameters resulting from the minimization procedure. The root-mean-square deviation of temperature was defined as follows:

$$\sigma_T = \left(\sum_{i=1}^{n} \frac{(T_i^{exp} - T_i^{cal})^2}{n-2}\right)^{1/2} \quad (5)$$

where n is the number of experimental points.

The pure component structural parameters r (volume parameter) and q (surface parameter) in UNIQUAC were obtained by the following expressions:

$$r_i = 0.029281 V_{m,1}, \qquad Zq_i = (Z-2)r_i + 2 \quad (6)$$

where Z denotes the coordination number (it was assumed that $Z = 10$) and the bulk factor l_i was assumed to be equal to 1 for the globular molecule.

The correlation results, the calculated values of the equation parameters and corresponding root-mean-square deviations of the systems {drug (1) + water, or alcohol (2)} obtained by three models are shown in Table 11.

The results of the correlation for these systems are also shown in Figs. 1–6. For the systems presented in Table 11, the average standard deviation of the correlation of solid–liquid-equilibrium with two-parameters Wilson, NRTL and UNIQUAC equations were $\sigma_T = 2.90$ K, $\sigma_T = 2.94$ K, and $\sigma_T = 2.71$ K, respectively.

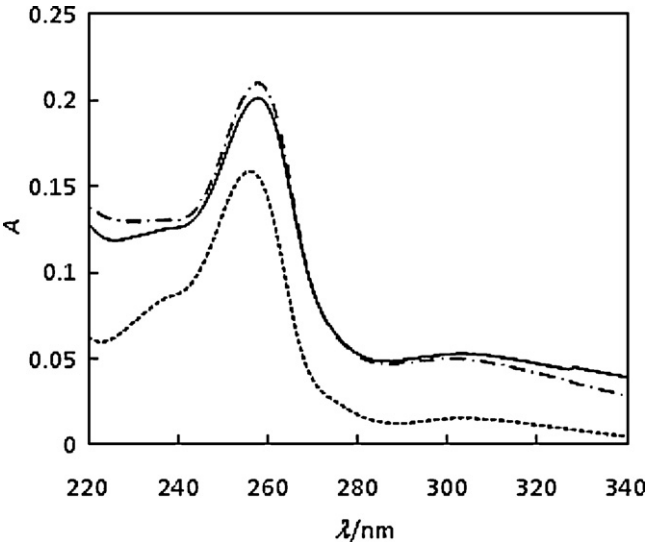


Fig. 9. pK_a measurements (absorbance vs. wavelength): experimental points for {fluphenazine dihydrochloride + water} mixtures: (—) buffer; (···) 0.1 M HCl; (– · –) 0.1 M NaOH.

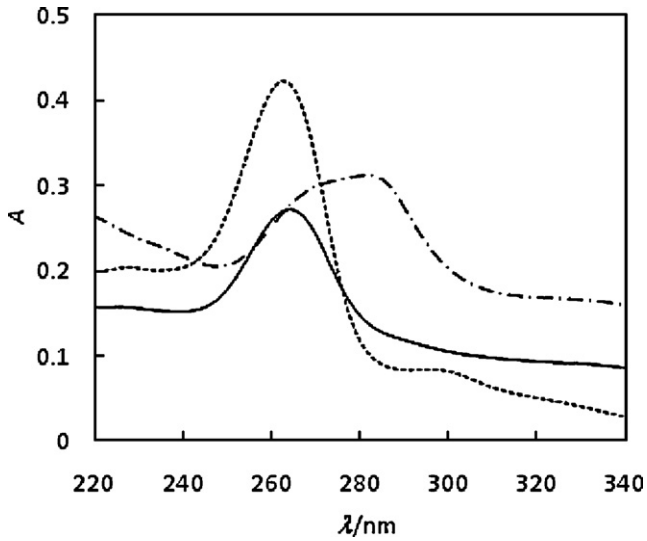


Fig. 11. pK_a measurements (absorbance vs. wavelength): experimental points for {thioridazine hydrochloride + water} mixtures: (—) buffer; (···) 0.1 M HCl; (– · –) 0.1 M NaOH.

Table 11
Results of correlation of the experimental solubility data of {drug (1) + solvent (2)} binary systems by means of the Wilson, NRTL[a], and UNIQUAC equations.

Drug	Solvent	Parameters			Root-mean-square deviations		
		Wilson	NRTL	UNIQUAC	Wilson	NRTL	UNIQUAC
		$\Delta\lambda_{12}\Delta\lambda_{21}$ (J mol^{-1})	$\Delta g_{12}\Delta g_{21}$ (J mol^{-1})	$\Delta u_{12}\Delta u_{21}$ (J mol^{-1})	σ_T (K)		
CHLPRO	Ethanol	−11,091.57 2059.10	−1054.17 −8547.88	1272.30 −2113.94	0.55	0.61	4.37
	1-Octanol	−1223.97 −1527.61	−133,422.78 −4930.51	−813.26 196.97	3.24	3.67	3.24
FLPHE	Ethanol	3623.25 −1981.00	−10,227.91 9510.32	−3432.35 5146.69	3.27	1.36	1.39
	1-Octanol	15,804.25 −4963.05	−11,179.89 22,259.50	−3580.83 5595.38	2.90	0.45	0.43
PRO	Ethanol	−7387.29 3439.55	1932.57 −5434.46	378.67 −538.19	3.93	3.82	6.08
	1-Octanol	−4317.50 2123.19	1734.44 −3754.98	547.63 −876.93	5.68	5.65	6.73
THRID	Water	6315.26 2279.77	1236.30 −6073.44	1214.81 2241.22	3.08	9.72	2.26
	Ethanol	−9910.49 117,167.29	−5912.60 8771.41	5265.48 −1900.53	1.61	1.60	1.49
	1-Octanol	2909.56 −1220.66	−1795.48 1240.53	−949.81 1093.50	1.33	1.32	1.32
TFLPER	Water	21,662.73 888.48	−918.51 −15,236.19	−1817.37 8569.72	6.60	1.04	5.19
	Ethanol	713.05 −387.18	−8583.20 13,224.13	−2400.42 3620.13	3.45	1.38	2.56
	1-Octanol	– –	−8789.70 17,130.65	−3282.67 5757.70	–	3.71	2.72
TFLPRO	Water	−23,159.93 2302.23	54,322.42 −18,092.15	– –	1.84	2.62	–
	Ethanol	2328.39 −4779.98	– –	– –	7.77	–	–
	1-Octanol	−9396.74 −2482.97	5136.70 −7262.90	−990.98 −1449.16	0.75	0.74	0.82

[a] $\alpha = 0.3$.

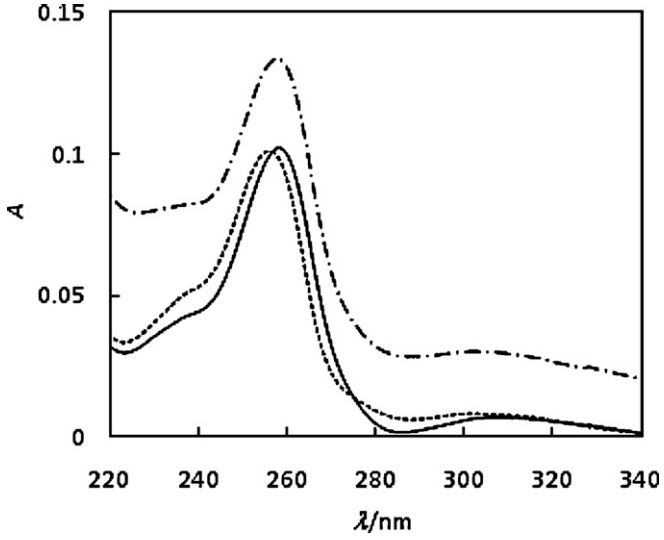


Fig. 12. pK_a measurements (absorbance vs. wavelength): experimental points for {trifluoperazine dihydrochloride + water} mixtures: (—) buffer; (···) 0.1 M HCl; (– · –) 0.1 M NaOH.

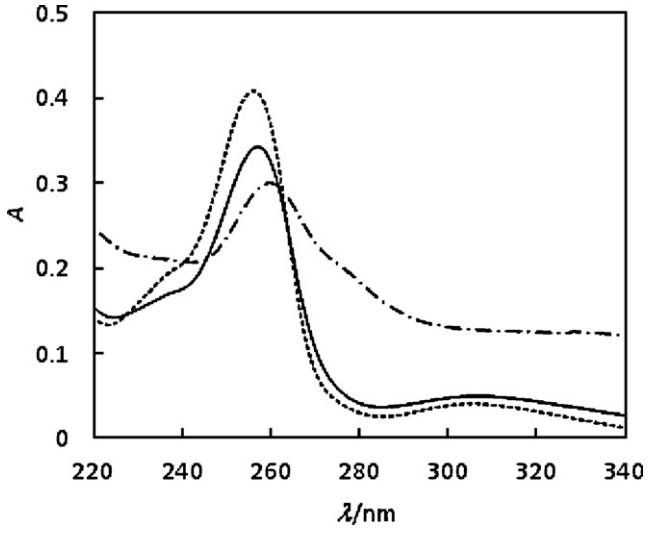


Fig. 13. pK_a measurements (absorbance vs. wavelength): experimental points for {triflupromazine hydrochloride + water} mixtures: (—) buffer; (···) 0.1 M HCl; (– · –) 0.1 M NaOH.

The deviations from ideality are negative, the solubility is higher than ideal solubility and the values of activity coefficients are lower than 1 ($\gamma_1 < 1$).

5. Conclusion

To the best of our knowledge the thermochemical data and solubility data for drugs chosen were not published. The differential scanning calorimetry (DSC) was employed to measure the enthalpy of melting, the melting temperature, the enthalpies of solid–solid phase transitions of two compounds, the glass transition temperature and heat capacity at the glass transition of measured hydrochlorides. The calorimetric and the solubility data were used to determine the activity coefficients of drugs measured at the saturated solutions in two, or three solvents.

As was expected, the solubility of chosen drugs were much higher in water than in alcohols. From the thermodynamic point of view, the solubility was higher than ideal solubility.

The new thermophysical data, the solubility and the pK_a data of six very important pharmaceuticals will enrich the data banks and will improve PK/PD prediction-methods development and precision.

The correlation of the solubility data was carried out by means of three commonly known G^E equations: with the Wilson, NRTL and UNIQUAC with the assumption that the systems studied here revealed simple eutectic mixtures with non-miscibility in the solid state. The obtained parameters may be useful for the extinction of the temperature range, or for the prediction of solubilities in the binary solvent mixtures.

Acknowledgement

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