Research Article

Physicochemical properties and solubilities of drug's hydrochlorides in water and alcohols

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ABSTRACT

This article is intended to combine different physico-chemical properties of three pharmaceuticals (Phs): Methoxyphenamine hydrochloride, Octopamine hydrochloride and Pargyline hydrochloride. This work aimed to: differential scanning calorimetry (DSC) analysis of chosen drugs; determine phase diagrams of binary systems of tested drugs with water and selected alcohols; use different mathematical models to describe the solubility equilibria curves; spectrophotometric and potentiometric determination of acidity constants of drugs in aqueous solutions; determine of the partition coefficient 1-octanol/water. All studied drugs are salts, and they have aromatic structure and functional groups, which supposed to reveal the different interaction with water and an alcohol. The solubility was determined with a dynamic method in three important solvents: water, ethanol and 1-octanol. Measurements were carried out mainly with a dynamic visual method. The UV-Vis spectrophotometric method was used in the binary system (octopamine·HCl + 1-octanol), because the solubility was very small. The obtained experimental data were correlated with the three excess molar free energy (G^{Ex}) equations: Wilson, NRTL and UNIQUAC. Tested Phs showed larger solubility in water than in alcohols, which means that they can be served to the human body in aqueous solutions. The measurements of constant acidity were made using the potentiometric and spectrophotometric (Bates–Schwarzenbach) method. Unfortunately, the pK_a data for methoxyphenamine·HCl and pargyline·HCl could not be found with a spectrophotometric method. Tests of constant acidity showed, which form of drug is active at some pH and provide guidance on drug dosage. In this work the partition coefficient 1-octanol/water for tested drugs was also determined. This coefficient is a measure of the hydrophilic/hydrophobic properties of the substance. Partition coefficient was measured by using the shake flask method, which consisted in dissolved test the substance in two solvents: 1-octanol and water. The values of the partition coefficients for all studied Phs are below unity, which shows a lipophobic character of these drugs.

Keywords: Solubility, thermodynamic correlation, p*K*a, octanol/water partition coefficients

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I. INTRODUCTION

Measurements of the physicochemical properties of the active substance are very important for pharmaceutical's (Phs) development because many drug candidates are synthesized annually in the pharmaceutical industry. Therefore, the characterization of early stages is needed to save time and money, since compounds without the relevant parameters will be further developed [1].

In this study we examined three Phs substances: methoxyphenamine hydrochloride, octopamine hydrochloride and pargyline hydrochloride. All drugs are salts. Phs investigated in terms of pharmaceutical activities belong to a class of drugs that affect the central nervous system. These drugs can act directly or indirectly on the nerve endings of autonomic nervous system. This system regulates the function of internal organs: cardiovascular system, digestion, metabolism, and directs many life processes, which are independent of our will. Octopamine is a compound naturally occurring in fruits of bitter orange [2,3]. This drug belongs to a class of drugs that stimulate adrenomimetic and α-receptors. The active substance raises directly pressure in the blood or through the release of norepinephrine. Octopamine has also been

known to increase the body's metabolism, resulting in the burning of calories. This drug also supports the insulin secretion and sensitivity [4]. The second drug, methoxyphenamine hydrochloride is a sympathomimetic amine. It is also known as 2-methoxy-N-methylamphetamine. This drug is a β-adrenergic receptoragonist of the amphetamine class used as a bronchodilator [5]. This drug stimulates the central nervous system and affects blood pressure. Methoxyphenamine drug, a compound which functions well as bronchodilator, is a frequently used in alleviating the bronchial asthma and symptoms of chronic obstructive pulmonary disease including cough, sputum and asthma. Pargyline hydrochloride belongs to a drug which inhibits the action of adrenergic receptors. This drug is a monoamine oxidase inhibitor of antihypertensive action. This results in a reduction in systolic and diastolic blood pressure [6]. This medicine reduces glomerulonephritis kidney filtration. It works slowly, but its effect is maintained over a long time after cessation of treatment. It can also be used in the treatment of hypertension particularly resistant to other treatment. The image of blood, urine and liver function during using pargilinie should be monitored [7].

The aim of this study was to examine the solubility of three drugs at constant pH in water, ethanol and 1-octanol. If the drug has to go through the layer of cells, the lining of intestinal wall must be soluble in the hydrophobic interior of the cell membrane. It means also high solubility of the drug lipids. Simultaneously, the drug should be soluble in water if it is to be dissolved in the intestine and blood. In this connection it must be a balance between hydrophobic and hydrophilic character. Very polar medicaments don't pass through the membrane and will not be absorbed. The less polar substances will slowly dissolve in water. This may cause slow absorption of the drug, because it allows to form a coagulated media in the intestine [8]. Solubility study of drugs in function of the temperature, being studied in the present work, are carried out infrequently, and they are mainly limited to the solubility of the drug in water or buffer systems at one temperature. A new trend is increasingly used in improving the drugs by the use of a complexing agent. It works by increasing the solubility of drugs that are poorly soluble in water and increasing their stability and bioavailability [9].

Comfortable drug candidates for testing methods and for the lipophilic character and acidity are necessary in modern pharmaceutical research and development strategy as well. Acidity constants are important in many analytical applications, such as the formation of complexes of metal ions with protic ligands, liquid extractions, and ion transport [10]. In this study, pK_a values were estimated by spectrophotometric Bates-Schwarzenbach method for all drugs using a UV-Vis spectrophotometer. Most drugs have ionization sites, that can be protonated or deprotonated at different pHs. If the drug has an amino group in its structure, may changes values of pK_a and can affect the ratio between its solubility in polar and non-polar solvent. Higher acidity constant value indicates the existence of a larger number of amine molecules ionized. The lower value of this parameter indicates the existence of larger amounts of free amine, and may show high solubility in non-polar environments. The pharmaceutical which will be served by mouth must dissolve in the polar and non-polar solvent. Therefore, the optimum value of pK_a corresponds to the equilibrium between the ionized and non-ionized form. Under physiological conditions this value is 7.4. Therefore, it is the pH value of blood. Drugs which pK_a values fall outside the range of 6-8 have the ability to act on ionized form and partially penetrate the cell membranes [11]. Moreover, the knowledge of the value of the constant acidity allows determining which form of the drug occurs in higher concentrations inside tissues. Often, due to the low solubility of drugs in aqueous solutions the study of pK_a values confirm considerable difficulties. The fact is quite significant that due to the low concentration of the drug, the potentiometric method of measurement is often burdened with a large error. Therefore, often measurements of the acidity constant are carried out by the spectrophotometry. This method has higher accuracy [12]. However, despite a number of advantages spectrophotometric methods, can't be applied to all substances. Currently, very often the theoretical calculation methods are the alternative to experimental methods.

Physicochemical properties of chemical compounds are associated directly with his biological activity. The most useful parameter in predicting the biological activity of a drug is the lipophilicity. It is characterized by the chemical affinity for the lipidic and aqueous phase. Moreover, the measure is the ratio of the equilibrium concentrations of a dissolved substance in two phase systems, which consist of two immiscible components. According to the Nernst's law, in thermal equilibrium conditions at a constant temperature and constant a pressure, the activity of the solute in each of solvents is constant. This value is called as the partition coefficient. The value of this factor depends on the activity of the solute in two solvents. It is a characteristic of two solvents' systems with solute, and depends on temperature and pressure. It is assumed that the best solvent's replicated system of polar and non-polar phases is water and 1-octanol. These mixed solvents are formed by two separated phases, wherein due to the partial mutual solubility does a system comprise 1-octanol saturated with water and water saturated with the 1-octanol. In this study, the value of the partition coefficient of 1-octanol/water was determined at the temperature T = 298.15 K. It is determined as a measure of the solubility of the compound in a lipid. The partition coefficient is defined as the ratio of a compound's concentration in 1-octanol to its concentration in water after the partition between two phases reaches equilibrium at a specified temperature [1]. The present article is the continuation of our systematic study on solubilities of drugs, the pK_a and the partition coefficient 1-octanol/water.

EXPERIMENTAL

Materials

The Phs were purchased from Sigma Aldrich, i.e. methoxyphenamine·HCl (CAS Registry No. 5588-10-3), octopamine·HCl (CAS Registry No. 770-05-8), and pargyline·HCl (CAS Registry No. 306-07-0), and were used without further purification. They were used as a powder or small crystals. The names, sources, purity, synonyms, CAS numbers, molecular formulas and molar masses of the compounds are listed in (**Table 1**). Structures of Phs are shown in (**Figure 1**). Remaining solvents, i.e. ethanol and 1-octanol, were obtained from Sigma Aldrich with a > 0.998 mass fraction purity. They were stored under freshly activated molecular sieves of type 4 Å. Water used as a solvent was twice distilled, degassed, deionized and filtered with Milipore Elix 3.

The buffers, 0.2 M hydrochloric acid and 0.2 M sodium hydroxide solution, were prepared from substances delivered by POCH, *i.e.* potassium dihydrogen phosphate (CAS Registry No. 7778-77-0; 0.995 mass fraction purity), disodium hydrogen phosphate (CAS Registry No. 7558-79-4; 0.99 mass fraction purity), borax (CAS Registry No. 1303-96-4; 0.988 mass fraction purity), sodium chloride (CAS Registry No. 7647-14-5; 0.999 mass fraction purity), monoethanolamine (CAS Registry No. 141-43-5; 0.995 mass fraction purity), hydrochloric acid (CAS Registry No. 7647-01-0; 0.35 mass fraction purity), and sodium hydroxide (CAS Registry No. 1310-73-2; 0.988 mass fraction purity). All solutes were filtrated twice with the Schott funnel with 4 μm pores.

Differential scanning calorimetry, DSC

Basic thermal characteristics of the Phs studied i.e. temperatures of fusion ($T_{fus,1}$) and enthalpy of fusion ($\Delta_{fus}H_1$) have been measured using a differential scanning microcalorimetry technique (DSC). The experiments were performed with DSC 1 STAR System (Mettler Toledo) calorimeter equipped with liquid nitrogen cooling system and operating in a heat-flux mode. The sample was sealed in ambient air in hermetic aluminium pans having mass of about 50 mg. Empty hermetic aluminium pan was used as a reference. Each sample size of about 10 mg was used throughout this study. The samples were heated in two separate furnaces. Experiments were carried out using 10 K min^{-1} heating rate. Calibration was done with 0.999999 mol fraction purity indium sample. The uncertainty of the melting temperature was ($T_{fus,1}$ ± 0.1) K and that of the enthalpy of fusion was ($\Delta_{fus}H_1$ ± 0.05) kJ·mol^{-1}. The thermophysical characteristic is given in (**Table 2**).

Table 1: Basic properties of Phs used in the investigations.

Name of compound	Source	Purity	Synonym / CAS Number	Molecular formula	Molar mass M/(g·mol^{-1})	Density ρ_{lit}/ρ_{exp} (298.15K) / (g·cm^{-3})	Refractive Index $n_{D}^{298.15}$
Methoxy phenamine ·HCl	Sigma Aldrich	≥ 0.99	2-Methoxy-N,α-dimethylbenzene ethanamine hydrochloride / 5588-10-3	$C_{11}H_{18}ClNO$	215.72	-	-
Octopamine· HCl	Sigma Aldrich	≥ 0.99	α-(Aminomethyl)-4-hydroxybenzyl alcohol hydrochloride, (±)-1-(4-Hydroxyphenyl)-2-amino-ethanol hydrochloride / 770-05-8	$C_8H_{12}ClNO_2$	189.64	-	-
Pargyline· HCl	Sigma Aldrich	≥ 0.99	N-Methyl-N-(2-propynyl)benzylamine hydrochloride, N-Methyl-N-propargylbenzylamine hydrochloride / 306-07-0	$C_{11}H_{14}ClN$	195.69	-	-
Water	Milipore Elix 3		dihydrogen monoxide	H_2O	18.01	0.99704[a]/ 0.99713	1.39276[b]
Ethanol	POCh	>0.998	ethyl alcohol / 64-17-5	C_2H_5OH	46.07	0.78504[c]/ 0.78511	1.35941[b]
1-Octanol	Sigma Aldrich	>0.998	alcohol C_8 capryl alcohol, octyl alcohol / 111-87-5	$C_8H_{17}OH$	130.23	0.82302[b]/ 0.82159	1.42760[b]

[a] lit. [13]; [b] lit. [14]; [c] lit. [15].

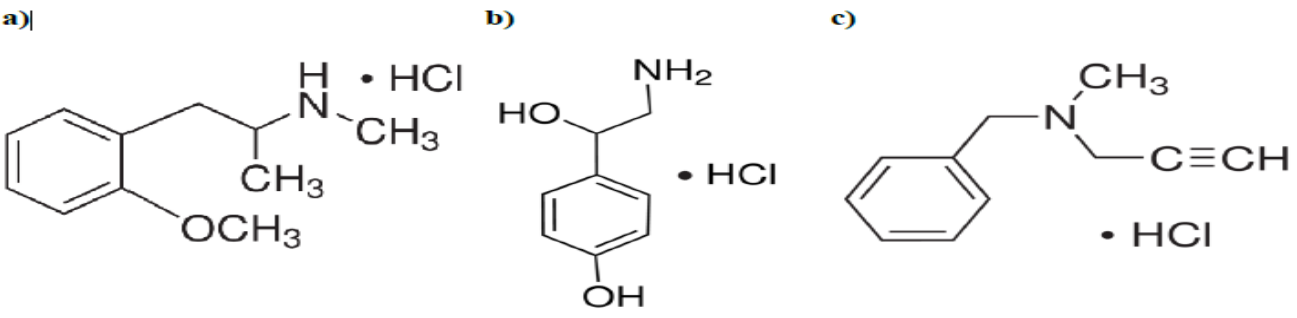


Figure 1: Structural formulae of: a) methoxyphenamine·HCl, b) octopamine·HCl, c) pargiline·HCl.

Table 2: Thermophysical chemical properties of the Phs with DSC: temperature and enthalpy of fusion, temperature and enthalpy of solid-solid phase transition and molar volume.

Phs	$T_{fus,1}$ (K)	$\Delta_{fus}H_1$ (kJ·mol^{-1})	$V_m^{298,15\,k}$ (cm^3·mol^{-1})[a]
Methoxyphenamine·HCl	400.8	53.97	233.7
Octopamine·HCl	426.3	30.74	170.3
Pargyline·HCl	431.4	28.33	219.4

Solubility measurements and apparatus

A dynamic (synthetic) method of the solubility measurements was used in the present work, according to all the procedures described in details previously [16,17].

The mixture (Ph + solvent) prepared by weighing the pure components with uncertainty of $1 \cdot 10^{-4}$ g; errors did not exceed $5 \cdot 10^{-4}$ in mole fraction. The sample was heated very slowly (at heating rate less than $2\ K \cdot h^{-1}$) with continuous stirring inside the Pyrex glass cell placed in thermostat. The crystal disappearance temperatures were detected visually and were measured with an electronic thermometer P550 (DOSTMANN Electronic GmbH). The thermometer was calibrated on the basis of ITS-90. The uncertainties of the temperature measurements were judged to be 0.05 K. Mixtures mass fraction errors did not exceed ± 0.0005. The reproducibility of the SLE measurements was ± 0.1 K. The results are listed in (**Tables 1S-3S**) in the Supplementary Material (SM).

One of the measured Ph revealed extremely low solubility in 1-octanol (octopamine·HCl). The visual method was not applicable, and the saturation shake-flak method with UV-Vis spectrophometer (Perkin-Elmer Life and Analytical Sciences Lambda 35, Shelton USA) was used. This method has been described previously [18].

pK_a Determination by potentiometric and spectrophotometric methods

The pK_a measurements were performed with Bates-Schwarzenbach the method [19] using the UV-Vis spectrophotometer (Perkin-Elmer Life and Analytical Sciences Lambda 35, Shelton USA). Measurements were conducted at two temperatures: T = 298.15 K and T = 310.15 K. Solutions of each Ph were prepared with mol concentration $1 \cdot 10^{-5}$ mol·dm^{-3}. For each Ph, three samples were prepared: in a buffer solution, in 0.2 M hydrochloric acid solution and in 0.2 M sodium hydroxide solution, and were scanned with water-buffer, 0.2 M water-acid and 0.2 M water-base solutions as a reference, respectively, with scan step 1 nm from 320 nm to 190 nm.

The pK_a values have been calculated by the following equation:

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

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

Three buffers were prepared (mol concentration) i.e., potassium dihydrogen phosphate (0.01000) and disodium hydrogen phosphate (0.01000; buffer, pH = 7.0), borax (0.007780), sodium chloride (0.014430; buffer, pH = 9.2), monoethanolamine (0.08000) and hydrochloric acid (0.0400; buffer, pH = 9.7). Buffers were chosen on a basic literature pK_a data in pH for the drug cited [19]. Values of an acidity functions $p(a_H\gamma_{Cl})$) and ionic strength (I) for used buffers are listed in (**Table 3**). The pK_a values were calculated, and the error of this measurement, calculated with the Gauss method is u (pK_a) = ±0.025.

Table 3: Values of an acidity functions ($p(a_H\gamma_{Cl})$) and ionic strength (I) for buffers [19].

Buffor, pH	T (K)	($p(a_H\gamma_{Cl})$)	I
7.0	298.15	7.080	0.020
	310.15	7.058	
9.2	298.15	9.237	0.015
	310.15	9.142	
9.7	298.15	9.629	0.020
	310.15	9.290	

Shake-flask determination of partition coefficients

K_{OW} values of Phs were directly determined using the so-called shake-flask method. The solute was partitioned between two liquid phases of the proposed solvent's system. in a test tube. After equilibrium, the relative concentration in each layer was determined with a spectroscopic method. The apparatus consisted of a jacketed glass cell of a volume of 10 cm^3 with a coated magnetic stirring bar, and closed to avoid absorption of pollutions from the atmosphere or losses of substances by evaporation was used. The jacket was connected to a thermostat bath (LAUDA Alpha A12) to maintain a constant temperature of (298.15 ± 0.02) K in the vessel. Both 4 cm^3 1-octanol and 4 cm^3 water contained a known amount of the Ph were mutually saturated prior to the experiment by stirring for at least 12 hours, and then allowing phases to separate at about two days to guarantee that the equilibrium state was reached completely. After the phase separation, samples from both phases in equilibrium were taken using automatic pipette (BRAND Transferpette S 0.5-5 ml). Concentrations of Ph in each phase just saturated with octan-1-ol and water were measured using UV–vis spectroscopy (Lambda 35, PerkinElmer), which has a sensitivity of 0.01 absorbance units.

RESULTS AND DISCUSSION

Using differential scanning calorimetry (DSC) the thermophysical properties were measured of study drugs: the melting temperature ($T_{fus,1}$) and the melting enthalpy (Δ_{fus} H_1). The thermograph of drugs underlined very high temperatures of melting from $T_{fus,1}$= 400.84 K for methoxyphenazine·HCl to $T_{fus,1}$= 431.35 K for pargyline·HCl. The DSC technique shows that examined materials are characterized by similar values of the melting points. The values of enthalpy of fusion were in range from 28.33 kJ·mol^{-1} for pargyline·HCl to 53.97 kJ·mol^{-1} for methoxyphenazine·HCl. These are typical values for organic compounds. All studied drugs did not show a solid-solid phase transition, which is characteristic of quasi-drugs substances.

The study on three drugs: octopamine, metoksyfenamine and pargyline hydrochlorides in three solvents were presented: in water, ethanol and 1-octanol. All investigated drugs have aromatic structure and functional groups which supposed to reveal the different interaction with the water and the alcohol.

The water was used because human body is mainly composed of water, 1-octanol was used as a model of lipid and ethanol was used as solvent with intermediate properties. Nine binary systems studied {Phs (1) + solvent (2)} were maintained at atmospheric pressure. Measurements were carried out mainly with the dynamic method. Only for (octopamine hydrochloride + 1-octanol) system the UV-Vis spectrophotometric method was used. The results are presented in (**Figures 2-4**).

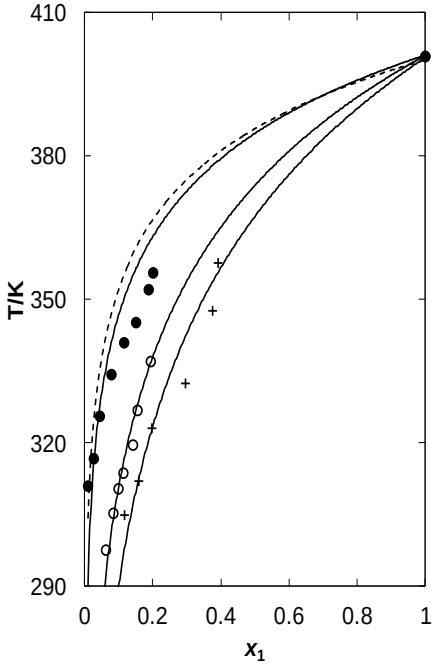


Figure 2: Experimental and calculated solubility of {methoxyphenamine·HCl (1) + solvent (2)} binary systems: (+) water, (○) ethanol and (●) 1-octanol. Solid lines (-) represents Wilson eq. for the water and ethanol and NRTL eq. for 1-octanol; the dotted line refers to the ideal solubility.

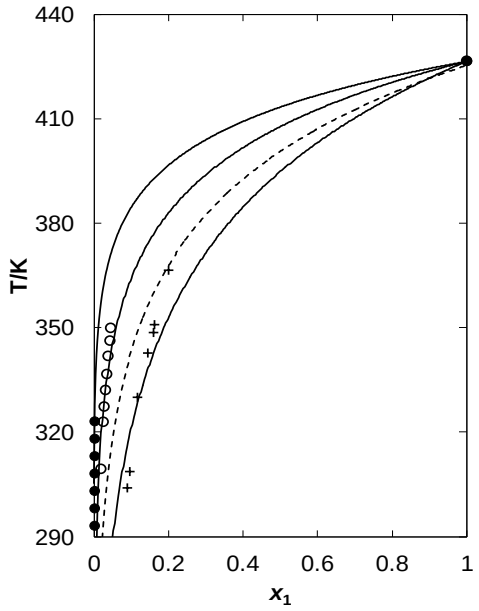


Figure 3: Experimental and calculatedsolubility of {octopamine·HCl (1) + solvent (2)} binary systems: (+) water, (○) ethanol and (●) 1-octanol. Solid lines (—) represents UNIQUAC eq.; the dotted line refers to the ideal solubility.

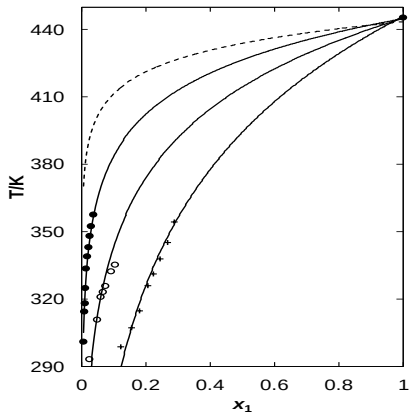


Figure 4: Experimental and calculated solubility of {pargyline·HCl (1) + solvent (2)} binary systems: (+) water, (○) ethanol and (●) 1-octanol. Solid lines (-) represents Wilson eq. for ethanol and 1-octanol, UNIQUAC eq. for the water; the dotted line refers to the ideal solubility.

Tested pharmaceuticals showed better solubility in water than in alcohols, which means that they can be served in aqueous solutions. The experimental solubility of all Phs in water is higher than the ideal solubility. The experimental solubility of methoxyphenazine·HCl and pargyline·HCl is higher than the ideal in all, three solvents. That means that the solubility of the octopamine·HCl in ethanol or 1-octanol is lower than ideal solubility. All drugs show better solubility in ethanol than in 1-octanol.

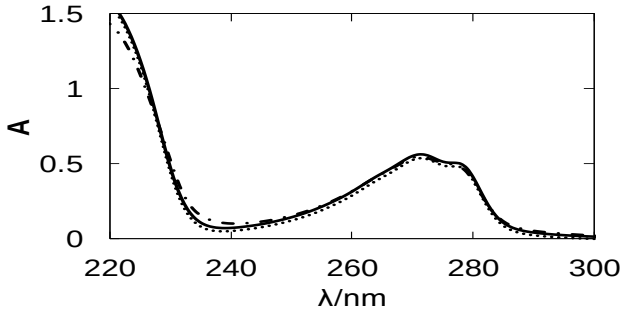
Measurements of constant acidity were made using potentiometric and spectrophotometric (Bates–Schwarzenbach) methods. For methoxyphenamine and pargyline pK_a could not be found with the spectrophotometric method. It was not possible because values obtained by spectrophotometric absorbance wavelength for the three solutions (buffer, 0.2 M HCl, 0.2 M NaOH) coincided. The pK_a values, which were obtained with the potentiometric method for methoxyphenazine·HCl and for pargyline·HCl are slightly lower than those in a literature for these drugs. Our experimental values of pK_a for octopamine·HCl, which were measured using potentiometric method are minimally lower than literature data or higher when the values were measured using the spectrohotometric Bates-Schwarzenbach method. Tests of constant acidity show, which form of drug is active at some pH and provide guidance on drug dosage. Our experimental results are showed in (**Table 4**) and in (**Figures 5-7**).

Table 4: Experimental and literature values of pK_a.

Phs	pK_a^{lit}	pK_a^{exp} (spectro.)	pK_a^{exp} (poten.)	T (K)	Buffer/pH
Methoxyphenamine·HCl	10.45[a,b,c]	-	10.36	298.15	9.7
		-	-	310.15	9.7
Octopamine·HCl	8.88[d] 9.54[e]	8.98 ± 0.02	8.87	298.15	9.2
		8.66 ± 0.02	-	310.15	9.2
Pargyline·HCl	6.6[f]	-	6.58	298.15	7.0
	6.9[g]	-	-	310.15	7.0

[a] lit. [20], [b] lit. [21], [c] lit. [22], [d] lit. [22], [e] lit. [24], [f] lit. [25], [g] lit. [26] . Standard uncertainties u are as follows: u(pK$_a$) = 0.0025, u(pH) = 0.1.

a)



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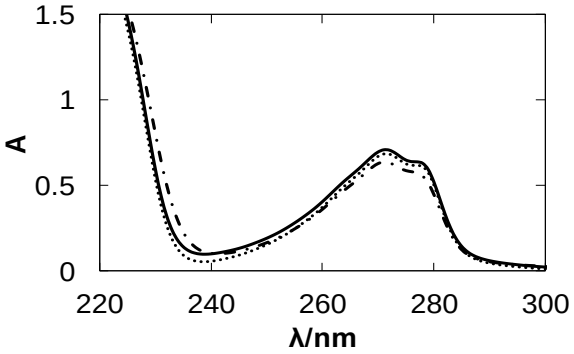
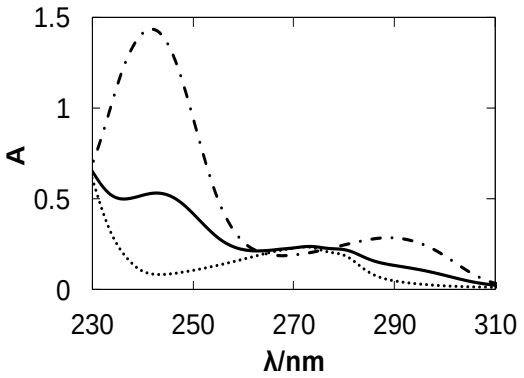


Figure 5: UV-Vis spectra (absorbance as a function of wavelength) for acidity constant measurement, a) at *T* = 298.15 K, b) at *T* = 310.15 K: experimental line of {methoxyphenamine·HCl + solvent}: (—) buffer; (····) 0.1 M HCl; (- · -) 0.1 M NaOH.

a)



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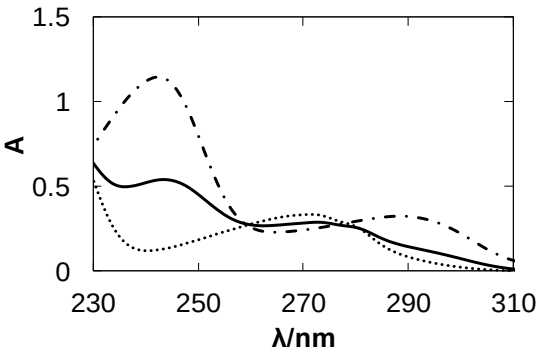
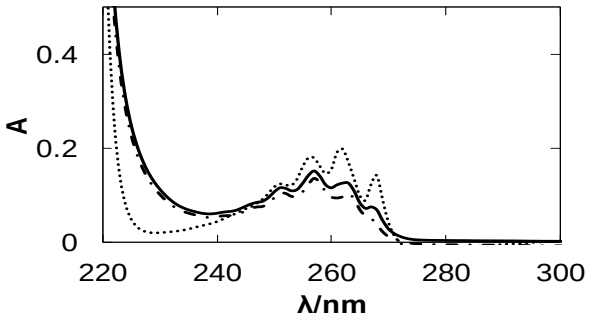


Figure 6: UV-Vis spectra (absorbance as a function of wavelength) for acidity constant measurement, a) at *T* = 298.15 K, b) at *T* = 310.15 K: experimental line of {octopamine·HCl + solvent}: (—) buffer; (····) 0.1 M HCl; (- · -) 0.1 M NaOH.

a)



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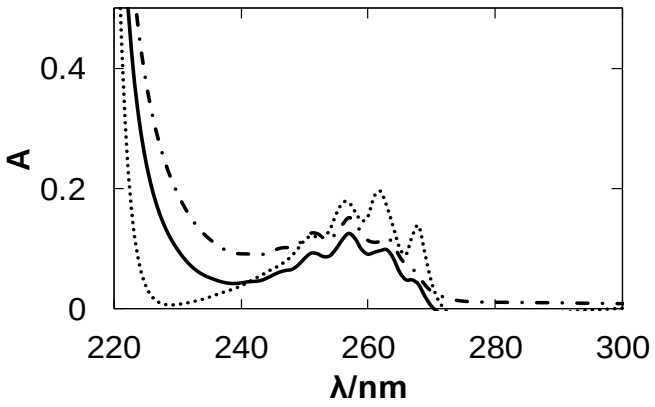

Figure 7: UV-Vis spectra (absorbance as a function of wavelength) for acidity constant measurement, a) at *T* = 298.15 K, b) at *T* = 310.15 K: experimental line of {pargiline·HCl + solvent}: (—) buffer; (····) 0.1 MHCl; (- · -) 0.1 M NaOH.

According to the octanol-water partition coefficient data of Phs, it is possible to predict lipo/hydrophilicity properties of examined drugs [23]. Obtained correlations for Methoxyphenamine hydrochloride, Octopamine hydrochloride and Pargyline hydrochloride show K_{OW} in range below unity from 0.013 for Methoxyphenamine hydrochloride to 0.074 for Octopamine hydrochloride, what proves hydrophilic properties for every of them. That properties can be a reason of process named bioconcentration of this drugs inside aquatic organisms exposed to the contact with Phs. What is more, low level of lipophilic properties of examined biopharmaceutics inhibits its absorption into cells through the lipophilic membrane. Ropel and coworkers have shown the influence of alkyl chains in molecular structures of substance for octanol-water partition coefficient, that why molecular structures of examined Phs is the reason of its lipophobic properties (**Figures 8-10**) [27].

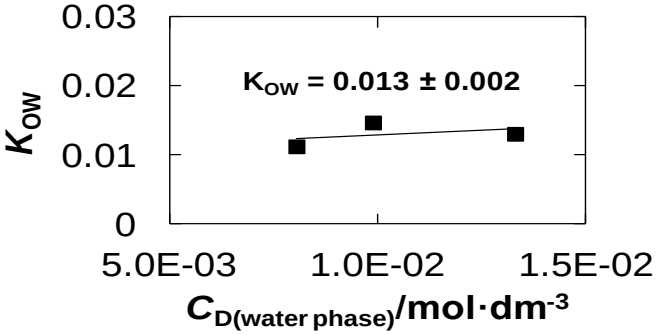

Figure 8: Variation of methoxyphenamine·HCl the octanol/water partition coefficient with concentration at T = 298.15.

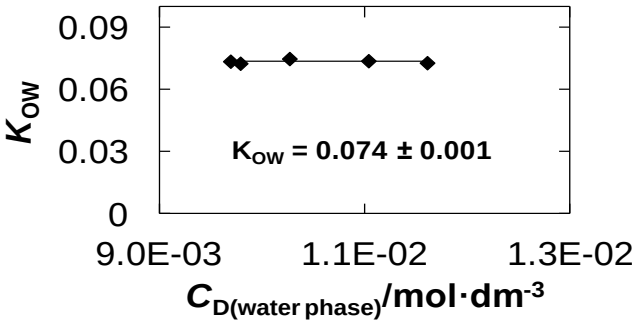

Figure 9: Variation of octopamine·HCl the octanol/water partition coefficient with concentration at T = 298.15.

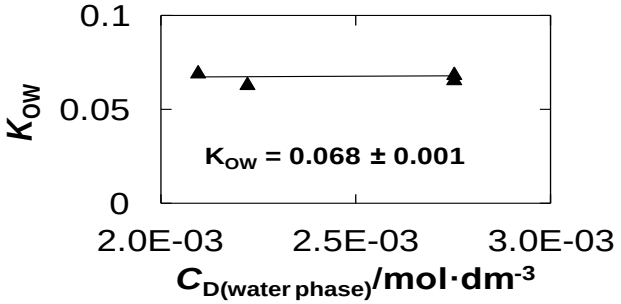

Figure 10: Variation of pargiline·HCl the octanol/water partition coefficient with concentration at *T* = 298.15.

MODELING

This work concerns about the use of mathematical models to describe physicochemical properties of biologically active compounds. The description of solid-liquid phase equilibrium (SLE) can be made for each component presented at the equilibrium with reference to the composition in both phases with the non-ideality of the phases and the thermophysical properties of pure components. The SLE is representing by the following equation [28]:

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

or in simple form

$$\ln x_1\gamma_1(x_1,T) = -\frac{\Delta_{fus}H_1}{R}\left(\frac{1}{T}-\frac{1}{T_{fus,1}}\right) \qquad (3)$$

Where: x_1 is the mole fraction solubility, activity coefficient γ is the function of solvent composition. $\Delta_{fus}H_1$ enthalpy of fusion of the pure drug, $\Delta_{fus}C_{p,1}$ is the difference between the heat capacity of the liquid and the solid at melting temperature, T , $T_{fus,1}$ represent equilibrium temperature and melting temperature.

When $\Delta_{fus}C_{p,1}$ is not known, the equation (3) is used, where the part connected with the solid-solid transition is not shown.

The Root-Mean-Square Deviation (RMSD) of temperature, σ_T, has been calculated according to the following definition:

$$\sigma_T = \left\{\sum_{i=1}^{n}\frac{\left(T_{exp,i}-T_{calc,i}\right)^2}{n-2}\right\}^{1/2} \qquad (4)$$

The correlation of the experimental curves was made using three predictive local composition models: Wilson [29], NRTL [30] and UNIQUAC [31]. They ensure a very good description of the composition of phases in equilibrium, with the fraction of crystallized solution. This equation is based on the thermodynamics of fluid-phase equilibrium. They describe the excess Gibb's energy as a function of the composition and the temperature. This may be used for interpolation, extrapolation and prediction in multi-component systems [32]. The Wilson and the UNIQUAC models have two binary interaction parameters. These parameters can be dependent on temperature. The NRTL equation has three parameters g_{ij} = g_{ji} and α_{ij}, which are referred to non-randomness factors. The parameters of correlation and standard

deviations are showed in (**Table 5**). The molar volumes of the Phs, which were calculated by the group contribution method described by Barton [16] are listed in (**Table 2**).

Table 5: Results of correlation of the experimental solubility of the {Ph (1) + solvent (2)} binary systems by means of the Wilson, NRTL, and UNIQUAC equations.

Phs	Solvent	Parameters			Rmsd's		
		Wilson	NRTL	UNIQUAC	Wilson	NRTL	UNIQUAC
		g_{12} - g_{11} g_{12} - g_{22}	Δg_{12} Δg_{21}	Δu_{12} Δu_{21}	σ_T	σ_T	σ_T
		(J · mol^{-1})	(J · mol^{-1})	(J · mol^{-1})	(K)	(K)	(K)
Methoxyphenamine· HCl	Water	-11851.66 3995.34	-2585.85[a] -6629.27	2184.69 3020.26	3.79	3.86	12.99
	Ethanol	-4922.87 -147.72	-4804.24[b] -398.92	1568.30 -2284.71	1.65	1.76	1.68
	1-Octanol	-3652.89 1879.92	913.05[c] -2504.23	-2687.97 5607.24	4.44	4.20	4.90
Octopamine · HCl	Water	-10203.46 23829.68	-2024.17[a] 1999.42	14820.93 -1575.37	9.28	11.98	4.45
	Ethanol	-2765.07 127760.07	-12542.48[d] 886.22	81765.21 -1586.46	4.11	4.60	2.16
	1-Octanol	7322.91 399189.46	12367.26[d] 8245.04	103589.22 -185.36	8.58	8.52	7.93
Pargyline · HCl	Water	-7150.26 3143.89	-7089.58[e] 3170.76	-491.07 1218.68	2.04	2.55	4.11
	Ethanol	-3012.89 2558.45	458.58[a] -986.25	1143.74 -468.48	1.44	1.48	1.46
	1-Octanol	1258.54 7387.82	8385.58[f] 2824.02	2209.47 -609.03	2.51	2.52	2.50

The Wilson model

In the binary system, the activity coefficient equation according to Wilson model is as follow:

$$n\gamma_1 = 1 - \ln\left(\sum_{j=1}^{n} x_j \wedge_{ij}\right) - \sum_{j=1}^{n} \frac{x_j \wedge_{ij}}{\sum_{k=1}^{n} x_k \wedge_{ij}} \qquad (5)$$

The Wilson equation presents the following expression for the excess Gibb's energy of binary solution [29].

Where: n - number of components; i-experimental point; x_j - mole franction; $\wedge_{ij}$ - parameter model. Binary interaction constants are defined as:

$$\wedge_{ij} = \frac{V_j}{V_i} e^{\left(\frac{-(\lambda_{ij}-\lambda_{ii})}{RT}\right)} \qquad (6)$$

The energies of interaction are $(\lambda_{ij} - \lambda_{ii})$ and they comply with the following expression: $\lambda_{ij} - \lambda_{ii} = \lambda_{ij} - \lambda_{ii}$. The mole values of solute and solvent are V_j and V_i.

NRTL model

The core of this theory is an extension of the local composition concept that accounts for the non-randomness of interactions. The activity coefficient of NRTL model is defined as:

$$n(\gamma_i) = \frac{\sum_{i=1}^{n} x_j \tau_{ji} G_{ji}}{x_j G_{ji}} + \sum_{i=1}^{n} \frac{x_j G_{ij}}{\sum_{k=1}^{n} x_k G_{ik}} \left[\tau_{ij} - \frac{\sum_{k=1}^{n} x_k \tau_{jk} G_{kj}}{\sum_{k=1}^{n} x_k G_{jk}}\right] \qquad (7)$$

Where: G_{ji} and τ_{ij} are the model parameters. The interaction energy parameter τ_{ij} to the i-j is expressed as:

$$\tau_{ij} = \frac{g_{ij} - g_{ii}}{RT} \quad (8)$$

The parameter G_{ij} is defined as:

$$G_{ij} = -\alpha_{ij}\tau_{ij} \quad (9)$$

Where: $g_{ij} = g_{ji}$ are binary parameters, α_{ij} is related to the non-randomness parameters of the mixture and it takes the values between 0.20 and 0.47 [33].

The UNIQUAC model

The UNIQUAC model is an extension of the quasi-chemical theory from Guggenheim for nonrandom mixtures containing components of different sizes [31]. In this model the excess Gibbs energy is defined as two contributions: a combinatorial term, which represents the influence of the structural parameters (differences in sizes and shapes between the components) and the second part is called as residual term. This part is account for the energy of interaction between segments. The UNIQUAC equation is:

$$G^E = \left(G^E\right)^C + \left(G^E\right)^R \quad (10)$$

where: $(G^E)^C$ – combinatorial part, $(G^E)^R$ – - residual part.

The combinatorial part follows as:

$$\left(G^E\right)^C = \sum_{i=1}^{n} x_i \ln\left(\frac{\varphi_i}{x_i}\right) + \frac{z}{2}\sum_{i=1}^{n} q_i x_i \ln\left(\frac{\varphi_i}{\xi_i}\right) \quad (11)$$

The residual part, follows as:

$$\left(G^E\right)^R = -\sum_{i=1}^{n} q_i x_{ij} \ln\left(\sum_{j=1}^{n} \xi_j \tau_{ij}\right) \quad (12)$$

According to this theory, the expression for the activity coefficient accept the form:

$$\ln(\gamma_i) = \ln\left(\gamma_i^C\right) + \ln\left(\gamma_i^R\right) \quad (13)$$

where:

$$\ln\left(\gamma_i^C\right) = \ln\left(\frac{\phi_i}{x_i}\right)\frac{z}{2} q_i x_i \ln\left(\frac{\phi_i}{\xi_i}\right) + l_i - \frac{\phi_i}{x_i}\sum_{j=1}^{n} x_j l_j \quad (14)$$

$$\ln\left(\gamma_i^R\right) = q_i\left(1 - \ln\left(\sum_{j=1}^{n} \xi_j \tau_{ji}\right) - \sum_{j=1}^{n} \frac{\xi_j \tau_{ji}}{\sum_{k=1}^{n} \xi_k \tau_{kj}}\right) \quad (15)$$

The volume parameter r_i and the surface parameter q_i in this model are defined as:

$$r_i = 0.029281 \cdot V_{m,1} \quad (16)$$

$$Z \cdot q_i = (Z-2) r_i + 2 \quad (17)$$

Where Z = 10 and denotes the coordination number and the bulk factor was assumed to be equal to 1 for the globular molecule.

CONCLUSIONS

We used differential scanning calorimetry (DSC) to measure the enthalpy of melting and the melting temperature of three measured coumponds. Summary of experimental data of the solubility and DSC allowed for the determination of activity coefficients of drugs in the three solvents. The phase equilibrium in binary systems had been measured for systems of {Ph (1) + water, or ethanol, or 1-octanol {(2)} at ambient pressure. Polar Phs may interact strongly with water and alcohols, which results in complete miscibility in the liquid phase (without miscibility gaps) and in most of the systems with the solubility higher than the ideal solubility. The results of the correlation of SLE with the two parameter Wilson equation were with acceptable standard deviation. New values of the pK_a were presented at two temperatures,
298.15 K and 310.15. K, which may found new applications in the future modelling process of these drugs. Finally, it was concluded that all Phs revealed similar solubility higher in water than in alcohols.

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