Solubility of Acetylsalicylic Acid in Ethanol, Acetone, Propylene Glycol, and 2-Propanol

Gustavo D. Maia*

Department of Chemical Engineering - DEQ, Federal University of São Carlos (Universidade Federal de São Carlos - UFSCar), São Carlos, Brazil

Marco Giulietti

Product and Process Technology Center CTPP, São Paulo, Brazil, Technological Research Institute - IPT, São Paulo, Brazil, and Federal Department of Chemical Engineering - DEQ, University of São Carlos (Universidade Federal de São Carlos - UFSCar), São Carlos, Brazil

As one of the most regularly traded-in medicines in the world, acetylsalicylic acid has been scarcely researched when in solution. This study is aimed at determining the solubility of acetylsalicylic acid in ethanol, acetone, propylene glycol, and 2-propanol, in addition to comparing their solubility values with the expected from an ideal solution. The solubility of acetylsalicylic acid is highest in acetone in all studied temperature ranges until T/K = 326.3. Propylene glycol presents lower solubility data in all studied temperature ranges. The solvent that presented the lowest average percent logarithmic deviation, concerning the ideality of the system, was ethanol, and the highest value of average percent logarithmic deviation was found in propylene glycol solutions. The experimental solubility data were correlated with the Nývlt model. We conclude that the Nývlt model is capable of representing properly the experimental data.

Introduction

The drug known as aspirin is an ordinary medicine that is easily found at any drugstore around the world. Little more than 100 years ago it was considered to be a miraculous drug that had just appeared at drugstores and pharmacies around Europe. Several similar components had already been produced, though none of them would ever be as successful as the component that is the active principle of aspirin, i.e., acetylsalicylic acid.

Currently, there have been countless reports on the benefits of a small dose of aspirin for the secondary prophylaxis of manifold cardiovascular diseases, such as brain stroke and myocardial infarction due to its capacity to inhibit the thromboxane synthesis, which prevents the formation of both brain and heart thrombi. It is also increasingly evident that aspirin, when regularly used, might play an important role in the prevention of colorectal cancer. Such a hypothesis was the topic of an evaluation presented by a working team at the International Agency for Cancer Research in Lyon, France.[1]

Especially in regard to solubility, a few researchers are exclusively concerned with obtaining values for a unique temperature without assessing the solubility in relation to temperature. The solubility is an important parameter to be determined because a series of processes depend upon its recognition, as in the event of crystallization. Its study initially faces the problem of a lack of information about the behavior of this substance in solution.

The behavior of the acetylsalicylic acid solubility in different temperatures affects, among other aspects, the choice of a crystallization, purification, and storage process. Florey[2] provides a series of solubility values for acetylsalicylic acid in certain solvents under a given temperature as well as physical and chemical properties of acetylsalicylic acid.

Hamer and Philips[3] describe one of the few solubility data for acetylsalicylic acid found in the literature. These authors studied the crystallization process of aspirin and determined its solubility in relation to temperature by employing acetone as solvent.

Therefore, this study is aimed at contributing toward the determination of the solubility of acetylsalicylic acid in four solvents, i.e., ethanol, acetone, propylene glycol, and 2-propanol, in different temperatures, in addition to comparing their solubility values with the expected from an ideal solution. The experimental solubility data were correlated with the Nývlt model.

In addition to the industrial relevance, the choice of the solvents was undertaken by taking into account the temperature range to obtain an enhanced distribution of temperatures for the solubility study.

Experimental Section

Reagent and Apparatus. The experimental apparatus used in the solubility determination was a polystat thermostatic Bath (by Cole Parmer, model 12101-20, series 709316) using distilled water as the circulation fluid, a support for the reactor, a 200 mL wrapped glass reactor, a gas propeller agitator, and agitation and control systems (by Applikon, ADI 1032, and Fisatom Scientific Equipment, model 713, respectively).

A digital analytical balance by Mettler Toledo A.G. (model PC 2000) at a precision of 0.001 g and a digital thermocouple by APPA MT-520 at a precision of 0.01 °C were used to measure the internal temperature of the reactor.

The analytical solvents used to study the solubility curves were: ethanol from Synth P.A. (99.5 % purity), acetone from

* Corresponding author. E-mail: gustavo.d.maia@gmail.com. Phone: (+55)-11-3767-4888.

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Table 1. Experimental Solubility x_{exptl}, Ideal Solubility x_{ideal}, LD_{ideal}, and LD_{calcd} for Acetylsalicylic Acid in Ethanol, Acetone, Propylene Glycol, and 2-Propanol

ethanol						acetone					
T/K	x_{exptl}	x_{ideal}	x_{calcd}	LD_{ideal}	LD_{calcd}	T/K	x_{exptl}	x_{ideal}	x_{calcd}	LD_{ideal}	LD_{calcd}
276.3	0.025	0.039	0.025	−0.445	0.000	281.9	0.061	0.046	0.061	0.282	0.000
291.9	0.049	0.060	0.048	−0.203	0.021	290.6	0.075	0.058	0.074	0.257	0.013
302.4	0.071	0.080	0.071	−0.119	0.000	297.9	0.088	0.071	0.088	0.215	0.000
310.0	0.093	0.098	0.092	−0.052	0.011	304.4	0.101	0.084	0.101	0.184	0.000
316.5	0.113	0.115	0.114	−0.018	−0.009	310.6	0.114	0.099	0.115	0.141	−0.009
321.5	0.133	0.131	0.133	0.015	0.000	315.3	0.127	0.112	0.128	0.126	−0.008
325.9	0.152	0.147	0.151	0.033	0.007	319.8	0.139	0.126	0.140	0.098	−0.007
330.4	0.170	0.165	0.171	0.030	−0.006	323.3	0.151	0.137	0.151	0.097	0.000
333.4	0.187	0.177	0.186	0.055	0.005	326.3	0.162	0.148	0.160	0.090	0.012
336.6	0.204	0.192	0.202	0.061	0.010	–	–	–	–	–	–
propylene glycol						2-propanol					
T/K	x_{exptl}	x_{ideal}	x_{calcd}	LD_{ideal}	LD_{calcd}	T/K	x_{exptl}	x_{ideal}	x_{calcd}	LD_{ideal}	LD_{calcd}
295.7	0.017	0.067	0.017	−1.371	0.000	281.6	0.013	0.045	0.014	−1.242	−0.074
301.1	0.025	0.077	0.025	−1.125	0.000	291.8	0.032	0.060	0.030	−0.629	0.065
305.1	0.033	0.086	0.033	−0.958	0.000	304.1	0.063	0.083	0.062	−0.276	0.016
308.2	0.041	0.093	0.040	−0.819	0.025	312.9	0.091	0.105	0.093	−0.143	−0.022
313.6	0.056	0.107	0.055	−0.647	0.018	316.1	0.102	0.114	0.106	−0.111	−0.038
318.3	0.071	0.121	0.071	−0.533	0.000	320.4	0.118	0.128	0.123	−0.081	−0.041
323.7	0.092	0.139	0.093	−0.413	−0.011	322.7	0.128	0.135	0.132	−0.053	−0.031
327.9	0.112	0.154	0.112	−0.318	0.000	325.8	0.143	0.146	0.144	−0.021	−0.007
330.7	0.126	0.166	0.126	−0.276	0.000	327.7	0.153	0.154	0.152	−0.007	0.007
333.9	0.145	0.179	0.143	−0.211	0.014	330.2	0.167	0.164	0.161	0.018	0.037

Synth P.A. (99.9 % purity), 2-propanol P.A. from Synth (99.9 % purity), and propylene glycol from Synth P.A. (99.9 % purity). The solute used was acetylsalicylic acid from Anidrol (99.5 % purity).

Experimental Procedure. The solubility, or saturation condition, is experimentally determined by heating the suspension and observing the temperature at which the entire solid melts.[6] Above this temperature, the solution is said to be subsaturated; i.e., the entire solute remains dissolved. However, it is possible to cool the same solution at temperatures below the saturation temperature without leading to crystallization. In this case, the solution is known as oversaturated.

Thus, for the determination of acetylsalicylic acid solubility curves and aiming at minimizing the effects of the metastable zones, which could hide the real acetylsalicylic acid solubility, the polythermic method proposed by Nývlt[6] was used.

This method comprises the preparation of a solution with 50.0 g of solvent and a given mass of acetylsalicylic acid. The reactor was connected to the thermostatic bath hoses, and the system underwent a 750 rpm agitation.

By satisfactorily regulating the bath temperature, the solution was then warmed up within the maximum rate for the bath until the crystals fully disappeared. Next, the bath temperature was regulated so that the solution was cooled, also under the maximum cooling rate possible for the bath to observe the formation of the first crystals.

Once the first crystalline nuclei were created, the bath was regulated to provide a temperature increase of 0.6 °C·h^{-1} until all the crystals found in the solution disappeared. Then the equilibrium temperature values were determined for the given solution.

Physical and chemical property values were obtained through the studies performed by Florey[2] (molecular weight, w/g·mol^{-1} = 180.15; fusion temperature, T_f/°C = 143) and Kirklin[7] (Δh^f/J·mol^{-1} = 29 800.00; Δc_p/J·mol^{-1} = 90.81).

Ideal Solubility and Nývlt Model. The temperature dependence of solubility in pure solvents, considering the system as ideal, can be described by a general solubility equation as follows

$$\ln\left(\frac{1}{x_1}\right) = \frac{\Delta h^f}{RT_f}\left(\frac{T_f}{T} - 1\right) - \frac{\Delta c_p}{R}\left(\frac{T_f}{T} - 1\right) + \frac{\Delta c_p}{R}\ln\frac{T_f}{T} \quad (1)$$

where R is the gas constant; T_f is the fusion temperature; T is the study temperature; Δc_p corresponds to the thermal capacity variation between the liquid and the solid phases; Δh^f is the fusion enthalpy; x is the molar fraction, or solubility; and the index 1 stands for the solute. So we can calculate the ideal solubility in any desired temperature range.[4,5]

In the model proposed by Nývlt,[6] the author considered a binary system where component 1 does not form solid solutions

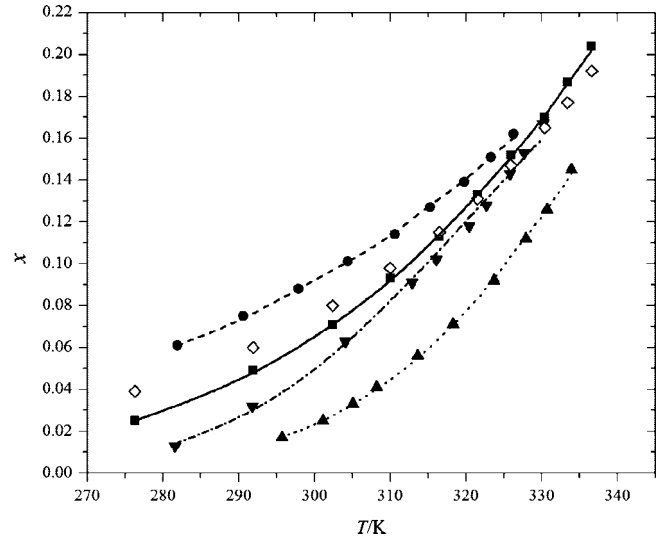

Figure 1. Comparative data of the solubility x as a function of temperature T/K to acetylsalicylic acid solutions in: ■, ethanol; •, acetone; ▲, propylene glycol; ▼, 2-propanol; ◊, ideal; and calculated data by the Nývlt model to acetylsalicylic acid solutions in —, ethanol; ---, acetone; -·-, propylene glycol; and ····, 2-propanol.

Table 2. Parameters of the Nývlt Model, N_1, N_2, and N_3, rmsd, APD_{ideal}, and APD_{calcd} for Acetylsalicylic Acid in Ethanol, Acetone, Propylene Glycol, and 2-Propanol

solvent	N_1	N_2	N_3	10^3rmsd	$APLD_{calcd}$	$APLD_{ideal}$
ethanol	27.769	−2500.906	−8.323	1.265	0.679	10.305
acetone	−21.826	198.466	8.125	0.000	0.550	1.657
propylene glycol	207.230	−11755.396	−68.500	0.949	0.674	66.714
2-propanol	255.456	−13368.498	−85.663	2.214	3.372	25.803

with the solvent. The equilibrium thermodynamic condition at constant pressure is the equality of chemical potentials, μ, of the components in both phases. On the basis of this consideration, the authors elaborated an expression that establishes a straight relation between the solubility of a given substance and the system temperature so that the activity coefficient would not explicitly appear in the equation, although it is contained within the adjustable parameters N_1, N_2, and N_3.

$$\log x = N_1 + \frac{N_2}{T} + N_3 \log(T) \tag{2}$$

Results and Discussion

The experimental solubility data of acetylsalicylic acid (x_{exptl}) in ethanol, acetone, propylene glycol, and 2-propanol were presented in Table 1. From Table 1, it can be found that the solubility in the four solvents increases with increasing temperature. The solubility of acetylsalicylic acid is the highest in acetone in all temperature ranges until T/K = 325.0. Propylene glycol presents the lower acetylsalicylic acid solubility data in all temperature ranges. The logarithmic deviations (LD_{ideal}) = $\ln(x_{exptl}/x_{ideal})$, between the experimental solubility and the ideal solubility, are also given in Table 1. Comparative solubility data as a function of temperature to acetylsalicylic acid solutions were presented in Figure 1.

The ideal solubility of acetylsalicylic acid was calculated for the four solvents, and the average percent logarithmic deviations (APLDs) related to experimental data are listed in Table 2. The APLDs are defined as

$$APLD_{ideal} = \frac{100}{N}\sum_{i=1}^{N}\left|\ln\frac{x^i_{exptl}}{x^i_{ideal}}\right| \tag{3}$$

$$APLD_{calcd} = \frac{100}{N}\sum_{i=1}^{N}\left|\ln\frac{x^i_{exptl}}{x^i_{calcd}}\right| \tag{4}$$

where N is the number of experimental points; x^i_{calcd} represents the solubility calculated by the Nývlt model; x^i_{exptl} represents the experimental solubility; and x^i_{ideal} represents the ideal solubility calculated.

Experimental solubility values of acetylsalicylic acid in acetone compared with Hamer and Philips[3] data present an average percent deviation of 4.34 %, which was considered a good deviation.

From Table 2, it is seen that the acetylsalicylic acid solutions in ethanol present the lowest APD_{ideal}, describing a strong ideal behavior related to other solutions in this study. The propylene glycol solutions, however, present the highest APD_{ideal}.

From the values of LD_{ideal} listed in Table 1, it can be found that some specific data present behavior near from ideal, such as acetylsalicylic acid in ethanol above T/K = 310.0 and acetylsalicylic acid in 2-propanol above T/K = 325.8. Individually, 2-propanol at T/K = 327.7 presents the solubility data nearest to an ideal solution.

The optimized values of the parameters N_1, N_2, and N_3 and the root-mean-square deviations (rmsd) are listed in Table 2. The rmsd was defined as

$$\text{rmsd} = \sqrt{\frac{\sum_{i=1}^{N}(x^i_{exptl} - x^i_{calcd})^2}{N}} \tag{5}$$

The solubility of acetylsalicylic acid data found by the Nývlt model was calculated, and the values are listed in Table 1. Average logarithmic percent deviations ($APLD_{calcd}$) related to experimental data are listed in Table 2.

From the values of rmsd and $APLD_{calcd}$ listed in Table 2 and the values of $LD_{calcd} = \ln(x_{exptl}/x_{calcd})$ listed in Table 1, it can be seen that the calculated solubility shows good agreement with the experimental values. Therefore, the Nývlt model can be used to correlate the solubility data of acetylsalicylic acid in the four solvents. Calculated data by the Nývlt model to acetylsalicylic acid solutions were also presented in Figure 1.

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