SHORT REPORT

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Solubility of Stearic Acid in Various Organic Solvents and Its Prediction using Non-ideal Solution Models

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ABSTRACT: The solubility of stearic acid in ethanol, methanol, ethyl acetate, and acetone has been measured gravimetrically at various temperatures ranging from 301 to 313 K at atmospheric condition. The solubility of stearic acid in ethyl acetate was found to be the highest, followed by ethanol, acetone and methanol. All experimental data were correlated using non-ideal solution models, namely, the modified Apelblat and the Buchowski equations. The calculated results agreed well with the experimental data.

KEYWORDS: stearic acid, solubility, organic solvent, Apelblat equation, Buchowski equation.

Stearic acid (octadecanoic acid) is a saturated fatty acid derived from animal and vegetable fats and oils. In Malaysia, it is mainly produced by the oleochemical (palm oil) industry and it has been the primary fatty acid commodity for many years[1]. Stearic acid is used in the manufacture of pharmaceutical products. Recently, it has been used in the development of a drug delivery system, because it is considered to be inert, inexpensive, and biocompatible, as well as of a low toxicity[2]. In addition, stearic acid has been used for a *cyclosporine-A* drug carrier system[3], and for masking the bitter taste of pharmaceutical compounds[4].

Stearic acid has to be prepared in the form of lipospheres for application as a kind of drug delivery system. Lipospheres can be prepared using supercritical fluid technology which utilizes carbon dioxide as an antisolvent by means of co-precipitation. In deploying the co-precipitation process for production of lipospheres, stearic acid as a matrix and an active pharmaceutical ingredient (API), should be able to be dissolved in certain organic solvents. This condition implies that for successful production of lipospheres, solubility of the API and stearic acid must not be infinite[5]. It means that the introduction of supercritical carbon dioxide into the solution should propagate the recrystallization process of stearic acid and the API. Consequently, the solubility data of stearic acid and the API in a particular solvent is needed before employing the co-precipitation process. Furthermore, this information is also necessary in the selection of the most appropriate supercritical antisolvent methods that could be applied[6].

The solubility of stearic acid in several organic solvents had been studied by several research groups[7, 8 9, 10]. Ralston and Hoerr[11] pointed out that the differences in the purities of the stearic acid samples will result in different solubility value. It means that the actual solubility data of stearic acid for each system chosen is necessary to be determined.

This work is part of a research project for the production of stearic acid lipospheres at low temperature using supercritical fluid carbon dioxide. This work investigated the solubility of bulk stearic acid in several organic solvents and at temperatures near the critical point of carbon dioxide. This work also aimed to test the capability of selected solubility correlation models to correlate the experimental data. Two non-ideal solution models, namely the modified Apelblat equation and the Buchowski (λH) equation were chosen to correlate the value of solubility data as a function of temperature.

Stearic acid was purchased from Fluka (purity ³ 97%) and used as received without any further treatments. Absolute ethanol (Scharlau, >99.8%), anhydrous methanol (Mallinckrodt, >99.8%), ethyl acetate (Mallinckrodt, 100%), and acetone (Merck, 99.8%) were used as solvents without further purification.

The solubility of stearic acid was measured under isothermal-isobaric conditions. The experimental

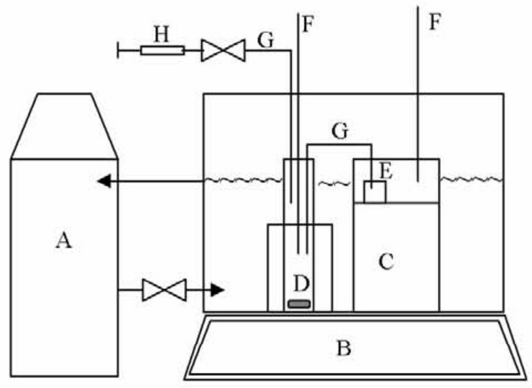

Fig 1. Schematic diagram of Isothermal Solubility Measurement Apparatus. (A) Thermoregulator and refrigerated bath; (B) Magnetic Stirrer; (C) Sampling Compartment; (D) Test Tube (Solvation System); (E) Weighing Bottle; (F) Thermometer; (G) Sampling line tubing; (H) Syringe.

apparatus used in this work is presented in Fig 1. Stearic acid in an excess amount was added into a test tube containing 25 mL of organic solvent. The test tube was placed into a constant temperature water bath. The temperature of the water bath was controlled by circulating thermostated water using a refrigerated bath (Techne-RB-5A, USA) and thermo regulator (Techne-RB-5A, USA). The temperature setting of the thermo regulator was calibrated previously to give the desired temperature in the test tube. The true temperature in the test tube was monitored by a mercury thermometer with an accuracy of 0.1 K. The mixture was then agitated using a magnetic stirrer. Stirring was stopped after 1.5 hours. The solution was then left for overnight, allowing undissolved solids to settle. Then, an approximately 4.0 g clear aliquot was transferred to a sample weighing bottle by pushing air into the test tube using a syringe. The solvent was then evaporated from the aliquot and the weight of the remaining solid was then determined. The solubility is determined based on the weight of the aliquot and the remaining solid. The balance used during the experimental work had an accuracy of 0.0001 g. The stearic acid solubility measurements were carried out at temperatures of 301, 303, 308, 311, and 313 K. Triplicates of each measurement were made to obtain reliable solubility values.

The melting temperature (m.p.) of the stearic acid used was determined by differential scanning calorimeter NETZSCH STA 409 C/CD (Selb/Bavaria, Germany) at a heating rate of 2 K/min from 298 to 373 K. Samples of stearic acid were prepared in platinum pans and purged with nitrogen at a rate of 50 mL/min. Pure indium was used for calibration, prior to measurement.

The dependence of stearic acid solubility in pure solvent on the temperature can be described by many thermodynamics approximation methods. Mirhemrabi and Rohani[14] employed the UNIQUAC model for describing the solubility behavior of stearic acid in organic solvents. Other models commonly used in solubility prediction based on non-ideal solution, are the modified Apelblat equation[15,16,17] and the Buchowski equation[18,19, 20].

The modified Apelblat equation can be expressed as follows:

$$\ln x_2 = a + \frac{b}{T} + c\ln T \tag{1}$$

where x_2 and T are the mole fraction of the solute and absolute temperature (K), respectively, and a, b, and c are the empirical constants. The c value represents the effect of temperature on the fusion enthalpy, as a deviation of heat capacity (ΔC_p). The value of constants a and b reflect the variation in the solution activity coefficient and provide an indication of the effect of solution non-idealities on the solubility of solute[17].

Buchowski *et al*[18] described the behavior of solid solubility in liquid as the Buchowski equation. This equation gave a good description for many solid - liquid systems using two adjustable parameters λ and H, as reported by previous researchers [19, 20]. The Buchowski equation can be written as:

$$\ln\left(1 + \frac{\lambda(1 - x_2)}{x_2}\right) = \lambda H\left(\frac{1}{T} - \frac{1}{T_m}\right) \tag{2}$$

where and H are two equation constants, T_m is the melting temperature of the solute (K), x_2 and T are mole fraction of solute and absolute temperature of the system (K), respectively. The value of reflects the non-ideality of the solution system, whereas H indicates the enthalpy of the solution[20].

In this work, both correlations were used to correlate the experimental solubility data. The adjustable parameters of the equations were optimised using Auto2fit software version 3.0 (CPC-X software). This software performs a non-linear curve fitting according to the Levenberg–Marquardt algorithm. This algorithm is an iterative process that stops when the fitting procedure converges. In this case, 5000 iterations with convergence tolerance of 1.0 $\times 10^{-10}$ were chosen.

The solubility of stearic acid with associated standard deviation (SD) in ethanol, methanol, ethyl acetate, and acetone are listed in Table 1. Table 1 also presents the difference between experimental and calculated solubility. It was found that the solubility values are dependent on the system temperature.

Table 1. Solubility of stearic acid in various organic solvents.

T(K)	Solubility			Error percentage $(x_2 - x_2^{cal}) \times 100/ x_2$	
	Experimetal $10^3(x_2 \pm SD)$	Predicted $(10^3.x_2^{cal})$			
		Modified Apelblat Equation	Buchowski equation	Modified Apelblat Equation	Buchowski equation
Ethanol					
301	10.5 ± 0.4	10.5	10.6	-0.1	-1.0
303	13.2 ± 0.4	13.4	13.4	-1.4	-1.7
308	23.9 ± 0.5	24.0	23.9	-0.5	0.0
311	34.2 ± 3.0	33.6	33.5	1.8	2.0
313	41.4 ± 1.2	41.8	41.9	-0.9	-1.1
Methanol					
301	2.7 ± 0.1	2.4	2.4	10.4	11.5
303	3.3 ± 0.1	3.2	3.2	3.6	4.2
308	6.1 ± 0.2	6.3	6.3	-3.0	-3.6
311	9.1 ± 0.2	9.5	9.5	-4.0	-4.2
313	12.7 ± 0.8	12.4	12.4	2.2	2.4
Ethyl Acetate					
301	13.9 ± 0.9	14.0	13.7	-0.6	1.3
303	17.7 ± 0.5	17.4	17.4	1.6	2.0
308	30.3 ± 0.7	30.4	30.8	-0.4	-1.7
311	42.9 ± 0.8	42.8	43.1	0.2	-0.4
313	54.0 ± 2.8	53.9	53.7	0.1	0.5
Acetone					
301	9.1 ± 0.1	8.8	8.7	3.2	3.8
303	11.3 ± 0.1	11.2	11.2	0.5	0.7
308	20.3 ± 0.1	20.6	20.7	-1.3	-1.7
311	29.3 ± 0.2	29.5	29.5	0.6	-0.8
313	37.6 ± 1.3	37.4	37.3	0.5	0.7

Increasing the system temperatures increased the stearic acid solubilities in all tested solvents.

Stearic acid is most soluble in ethyl acetate and least soluble in methanol. The solubility of stearic acid in four solvents in order of increasing solubility is methanol, acetone, ethanol and ethyl acetate. This solubility behavior may be explained by considering the polarity and hydrogen bonding properties of the system. As a fatty acid, stearic acid is a relatively non-polar compound. Therefore, based on the principle that "like dissolve like", stearic acid will be more soluble in non-polar solvents and less soluble in polar solvents. The polarity of solvent can be explained by Reichardt's normalized molar electronic transition energy (E_T^N)[12]. The polarity of solvents decreases from methanol, ethanol, acetone to ethyl acetate. The solubility order of stearic acid in methanol and ethyl acetate agrees with the polarity order of solvents, but it is not in the case for stearic acid solubility in ethanol and acetone. This is probably due to the effect of hydrogen bonding properties of ethanol. Ethanol has stronger hydrogen bonding characteristic than acetone[13]. Thus, stearic acid will be more favorable to dissolve in ethanol rather than in acetone.

The stearic acid solubility data obtained by different researchers were compared in Fig 2. It was obvious that the stearic acid solubility data obtained from this work were mostly higher than the published ones. These differences could be due to a different composition of stearic acid which is used, either its purity or its polymorphs. Hoerr and Ralston[11] stated that the presence of impurities can influence the solubility of primary fatty acid. One way to see the difference of stearic acid composition is from its m.p..

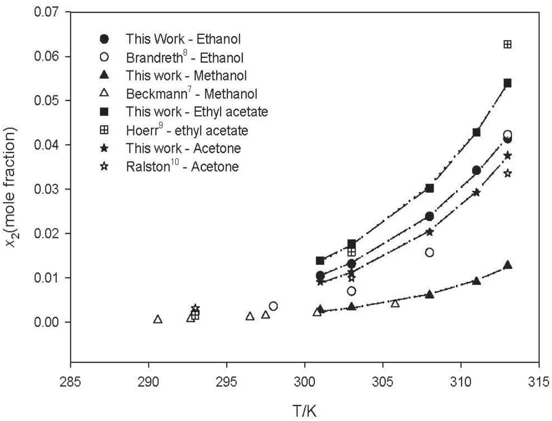

Fig 2. Comparison of experimental solubility of stearic acid in organic solvents with calculation using modified Apelblat (- -) and Buchowski (···) correlations.

The stearic acid used in this work has an m.p. of 342 K, whereas Brandeth and Johnson[8] used stearic acid with an m.p. of 339 K, and Hoerr and Ralston[10] used stearic acid with an m.p. of 342.2 K.

From the results shown in Table 1 and Fig 2, it can be observed that the Apelblat equation and the Buchowski equation gave almost the same goodness of fit to the experimental data. Error percentages of the predicted solubility values obtained from calculations using both models were below 5%, except for one point of stearic acid solubility in methanol. The goodness of fit of these equations can also be seen from the R^2 values listed in Table 2, which are almost unity. Buchowski *et al.*[18] stated that in an ideal solution, the value of equals to 1. The values of the obtained equation parameter (l) in Table 2 showed that the stearic acid – organic solvent solutions understandably were non-ideal. It could be caused by the tendency of stearic acid molecules in the solution to associate between themselves and by the difference of chemical structure between stearic acid and solvents. This agrees with Mirmehrabi and Rohani[14], who reported that solution of stearic acid in some organic solvents are highly non-ideal.

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Table 2. The optimized adjustable parameters of modified Apelblat and Buchowski equations for stearic acid in various organic solvents

	Modified Apelblat Equation				Buchowski Equation		
Solvent	a	b	c	R^2	λ	H	R^2
Ethanol	331.20	-24509	-44.56	0.99	0.7487	14287	0.99
Methanol	-541.26	13520	85.91	0.99	0.3915	32733	0.99
Ethyl Acetate	-799.98	27318	123.52	0.99	0.9750	10980	0.99
Acetone	-311.37	4363	51.19	0.99	0.7984	14202	0.99