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The Solubility of Beclomethasone-17,21-dipropionate in Selected Organic Solvents: Experimental Measurement and Thermodynamic Modeling

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Abstract:

In this study the solubility of beclomethasone-17,21-dipropionate in acetone, methanol, and ethanol as model systems to investigate the supercritical gas antisolvent micronization process was performed over a wide range of temperatures. Beclomethasone-17,21-dipropionate is an inhaled steroid used for the treatment of asthma. Experimental determination of the solubility of beclomethasone-17,21-dipropionate in the three solvents was achieved by employing a gravimetric technique over the temperatures range 24.5−62.5 °C. The solubility data were modeled using the group contribution parameters and UNIversal QUAsi-Chemical (UNIQUAC) theory. The binary parameters of the UNIQUAC model were calculated by employing the experimental solubility data. Good predictions of the solubility measurements were achieved using the UNIQUAC model.

1. Introduction

Inhaled corticosteroids, such as beclomethasone-17,21-dipropionate, are well-established anti-inflammatory therapies for the treatment of asthma,[1] recommended in national treatment guidelines as first-line therapy for this chronic disease.[2] Asthma is an inflammatory disease affecting the entire bronchial tree, from the large central airways down to the small peripheral airways.[3,4] An optimal therapeutic response with inhaled corticosteroids using dry powder inhalers (DPIs) would, therefore, be obtained with a powder that reaches both the large and small airways of the lung.[5]

In this research the objective is to investigate the feasibility of supercritical crystallization processes such as the gas antisolvent crystallization process (GAS) to generate small particles of beclomethasone-17,21-dipropionate applicable for pulmonary inhalation therapy.[6] Thus, constructing the solubility profile of beclomethasone-17, 21-dipropionate in different solvents such as acetone, methanol, and ethanol is of high theoretical and empirical interest. Moreover, solid−liquid equilibria (SLE) or solubility over a wide range of temperatures is essential for the design of a separation process such as crystallization.[7]

In GAS, supersaturation is generated by expanding a solution with a supercritical fluid such as CO_2. Upon addition of high pressure CO_2, the solution is expanded, its solvent power is reduced, and precipitation is triggered.

A supporting thermodynamic model is necessary to correlate, predict, and interpolate solubility measurements. Moreover, prediction of solid−liquid equilibrium is important in chemical engineering applications, such as extraction and crystallization. The solubility of a solid depends on the physical properties of the solid and on its interaction with the liquid solvent. The prediction or correlation of the solubility in a liquid solvent requires a model for the activity coefficient that accurately takes into account the constitutive nature of the components in the mixture (i.e., activity coefficients in liquid can be calculated from a model, which expresses the excess Gibbs free energy of the mixtures as a function of the composition). However, several methods of phase equilibrium data correlation/prediction have been reported in the literature.[8−10]

A particularly useful model, applicable to a wide variety of liquid mixtures, was given by Abrams and Prausnitz;[11] this model, called UNIQUAC, uses only two adjustable parameters per binary in addition to pure-component parameters reflecting the size and outer surface area of the molecules.

Basically, there are two thermodynamic approaches for phase equilibrium calculations: one of them uses equations of state (EOS) to correlate equilibrium data; the other employs equality of fugacity with a model for the activity coefficient. Cubic equations of state are successfully used for phase equilibrium calculations. However, a single cubic EOS is generally not reliable in providing predictions for all volumetric, thermodynamic, and phase equilibrium properties for all type of fluids and mixtures.[12] Moreover, the representation of the solid−liquid equilibria of nonideal systems using EOS with ordinary parameters cannot provide reliable predictions as special mixing rules will be needed for the correlation and prediction of phase equilibrium properties.

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Table 1. **Physical properties of beclomethasone-17,21-dipropionate**

T_m °C	ΔH^m_{fus} (J/g)	$c_P = A + BT + CT^2 + DT^3$ (J/g·°C), range of 25−90 and 100−30 °C			
		A	B	C	D
98.17	84.93	2.0878	-3.2471×10^{-3}	6.3291×10^{-5}	-3.7953×10^{-7}
“Liquid”		5.2703	4.2192×10^{-5}	5.6871×10^{-2}	7.1384×10^{-8}

The UNIQUAC equation, which is an activity coefficient model, provides an excellent correlation of phase equilibrium for strongly nonideal systems, since it accounts for the molecular volume, specifically when molecular size differences reflected by the liquid molar volumes are considered appreciable. In addition, the UNIQUAC model accounts also for the surface area properties of all chemical species in the system. Moreover, a series of articles on the use of the UNIQUAC activity coefficient model for the correlation/prediction of solid−liquid phase equilibrium have been reported in the literature.[13−15]

The solubility of beclomethasone-17,21-dipropionate in selected organic solvents (acetone, methanol, and ethanol) is measured. Moreover, a predictive molecular thermodynamic study using the group contribution parameters and UNIversal QUAsi-Chemical (UNIQUAC) theory is carried out.

2. Experimental Section

2.1. Materials and Apparatus. The experimental setup for the gravimetric solubility determination experiments consists of a temperature-controlled refrigerated circulating bath (RTE-220, Neslab). A focus light (Leica CLS 150) was used for visual monitoring of the point of complete dissolution.

The organic solvents (analytical grade) were purchased from the Sigma-Aldrich Company. The beclomethasone-17,21-dipropionate used in this work was donated by Glaxo Smithkline Inc. (Mississauga, Canada). Thermal analysis was conducted by a differential scanning calorimeter (DSC, Mettler Toledo, Chicago, IL).

2.2. Gravimetric Determination of Solubility. The solubility of the beclomethasone-17,21-dipropionate in acetone, methanol, and ethanol was measured over a temperature range from 24.5 to 62.5 °C. The experimental determination of solubility was first approached from an undersaturated solution. Different masses of the solid solute were introduced to a certain volume of solvent in a glass vial. The vial was then immersed in the thermostatted water bath and given 30 min of gentle mixing for thermodynamic equilibrium to be achieved. The solubility temperature was determined visually as the system temperature at which the system remained homogeneous. Having determined the solubility values for a range of temperatures, the solubility data at a specified set of temperatures can consequently be easily determined. The possible solvent evaporation at higher temperatures and the visual determination of solubility could induce errors; therefore, in order to minimize the experimental error, the solubility determination experiments were conducted from both undersaturation and supersaturation. Experiments were repeated at least three times in order to ensure the accuracy of the measurements. The accuracy of the balance and thermometer were ±0.01 mg and ±0.1 °C, respectively. Moreover, thermal analysis of the beclomethasone-17,21-dipropionate was conducted by a differential scanning calorimeter. Samples weighing between 2−5 mg were prepared in a covered 40 mL aluminum crucible with a hole in the lid to allow venting. A heating rate of 0.5 °C /min for the determination of the melting temperature and heat of fusion was used. The sensors and the crucibles were under the flow of nitrogen during the experiment. The calibration of the instrument was performed using standard indium.

Table 2. **Heat capacity correlations for acetone, methanol, and ethanol[19]**

cmpd	$c_P = A + BT + CT^2 + DT^3$, J/mol·K			
	A	B	C	D
acetone	46.878	6.2652	-2.0761×10^{-3}	2.9583×10^{-6}
methanol	40.152	3.1041×10^{-1}	-1.2091×10^{-3}	1.4598×10^{-6}
ethanol	59.342	3.6358×10^{-1}	-1.2164×10^{-3}	1.8030×10^{-6}

Thermodynamic Modeling

3.1. Solid−Liquid Equilibrium. Applying the equilibrium criterion to the solid solute in the fluid mixture:

$$f_2^S(P, T) = f_2^F(P, T, x) \tag{1}$$

wheref_2^S and f_2^F are the fugacities of pure solid solute and the pure fluid, respectively.

For the solubility of a solid in the liquid phase, eq 1 can be rewritten as:

$$f_2^S(P, T) = x_2\gamma_2(P, T, x)\, f_2^L(P, T) \tag{2}$$

where x_2, and γ_2 are the mole fraction and the activity coefficient of the solid solute, respectively, and f_2^L is the fugacity of pure subcooled solvent.

According to Prausnitz *et al.*[16]

$$\ln\left(\frac{f_2^L}{f_2^S}\right) = \frac{-\Delta H^m_{fus}}{RT_m}\left(\frac{T_m}{T} - 1\right) + \frac{\Delta c_p}{R}\left(\frac{T_m}{T} - 1\right) - \frac{\Delta c_p}{R}\ln\left(\frac{T_m}{T}\right) \tag{3}$$

where T_m is the melting point. ΔH^m_{fus} is the heat of fusion and Δc_p is the difference in heat capacities of solid and liquid at temperature T. Heat capacity correlations for beclomethasone dipropionate, acetone, methanol, and ethanol are given in Tables 1 and 2, respectively.

Combining eqs 2 and 3 yields:

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$$\ln\left(\frac{1}{x_2\gamma_2}\right) = \frac{-\Delta H_{\mathrm{fus}}^{\mathrm{m}}}{RT_{\mathrm{m}}}\left(\frac{T_{\mathrm{m}}}{T} - 1\right) + \frac{\Delta c_{\mathrm{p}}}{R}\left(\frac{T_{\mathrm{m}}}{T} - 1\right) - \frac{\Delta c_{\mathrm{p}}}{R}\ln\left(\frac{T_{\mathrm{m}}}{T}\right) \quad (4)$$

For ideal solutions, the activity coefficient of the solute is equal to unity so that eq 4 can be rewritten as:

$$\ln\left(\frac{1}{x_2^{\mathrm{ideal}}}\right) = \frac{-\Delta H_{\mathrm{fus}}^{\mathrm{m}}}{RT_{\mathrm{m}}}\left(\frac{T_{\mathrm{m}}}{T} - 1\right) + \frac{\Delta c_{\mathrm{p}}}{R}\left(\frac{T_{\mathrm{m}}}{T} - 1\right) - \frac{\Delta c_{\mathrm{p}}}{R}\ln\left(\frac{T_{\mathrm{m}}}{T}\right) \quad (5)$$

and

$$x_2 = \frac{x_2^{\mathrm{ideal}}}{\gamma_2} \quad (6)$$

For nonideal solutions, γ_2 must be estimated from either experimental data or a liquid solution model. However, many empirical and semitheoretical equations exist for estimating activity coefficients of binary mixtures. For hydrocarbon mixtures of polar compounds, the UNIQUAC predictive theory is a powerful and a convenient model.

3.2. The UNIQUAC Model. The UNIQUAC thermodynamic model was employed to predict the solubility of beclamethasone dipropionate in acetone, methanol, and ethanol. The UNIQUAC equation like van Laar or Wilson equations is a two-parameter activity coefficient model. However, it is considered to have a better theoretical basis, although it is more complicated. The UNIQUAC expression for activity coefficients is given by:

$$\ln\gamma_i = \ln\gamma_i(\text{combinatorial}) + \ln\gamma_i(\text{residual}) \quad (7)$$

$$\ln\gamma_i(\text{combinatorial}) = \ln\left(\frac{\varphi_i}{x_i}\right) + \frac{z}{2}q_i\ \ln\gamma_i(\text{combinatorial}) = \ln\left(\frac{\varphi_i}{x_i}\right) + \frac{z}{2}q_i\ln\left(\frac{\theta_i}{\varphi_i}\right) + l_i - \frac{\varphi_i}{x_i}\sum_j x_j l_j \ln\left(\frac{\theta_i}{\varphi_i}\right) + l_i - \frac{\varphi_i}{x_i}\sum_j x_j l_j \quad (8)$$

where

$$\theta_i = \text{area fraction of species } i = {}^{x_iq_i}/_{\sum x_jq_j} \quad (9)$$

$$\varphi_i = \text{volume fraction of species } i = {}^{x_ir_i}/_{\sum x_jr_j} \quad (10)$$

$l_i = (z)/(2)(r_i - q_i) - (r_i - 1)$, and z is the average coordination number.

$$r_i = \text{volume parameter for species } i = \sum_k \upsilon_k^{(i)} R_k \quad (11)$$

$$q_i = \text{surface area parameter for species } i = \sum_k \upsilon_k^{(i)} Q_k \quad (12)$$

$\upsilon_k^{(i)}$, is the number of groups of type k in molecule i

$$\ln\gamma_i(\text{residual}) = q_i\left[1 - \ln\left(\sum_j \theta_j\tau_{ji}\right) - \sum_j \frac{\theta_j\tau_{ij}}{\sum_k \theta_k\tau_{kj}}\right] \quad (13)$$

where

$$\tau_{ij} = \exp\left(\frac{u_{ij} - u_{jj}}{RT}\right) = \exp\left[\frac{-a_{ij}}{T}\right] \quad (14)$$

where u_{ij} is a measure of the interaction energy for a species$i$−species j interaction.

4. Results and Discussion

Table 3 shows the results of the gravimetric solubility measurements of beclomethasone-17,21-dipropionate in acetone, methanol, and ethanol over the temperature range of 24.5−62.5 °C. The solubility gravimetric measurements had a maximum level of relative uncertainty of 4.4% in acetone, 4.6% in methanol, and of 5.1% in ethanol. Figure 1 shows the graphical representation of the solubility gravimetric measurements.

Employing the UNIQUAC thermodynamic model of eq 7, values of the two-parameter activity coefficient, γ_2, were computed for the whole temperature range 24.5−62.5 °C for the three solvents.

Using the experimental thermal properties of the pure solid and solubility data, the activity coefficient of the solute given the values of the difference in heat capacities of solid and liquid (Δc_{p}), heat of fusion ($\Delta H_{\mathrm{fus}}^{\mathrm{m}}$), and the melting point (T_{m}), was calculated with the assumption of ideal solution using eqs 5 and 6. The activity coefficient of the solute is given as a ratio of the ideal mole fraction of the solid solute to the experimental

Table 3. **Solubility of beclomethasone-17,21-dipropionate in selected organic solvents: acetone, methanol, and ethanol (the maximum level of relative uncertainty: 4.4% in acetone, 4.6% in methanol, and 5.1% in ethanol)**

temperature, °C	acetone, g_{solute}/100 g_{solvent}	methanol, g_{solute}/100 g_{solvent}	ethanol, g_{solute}/100 g_{solvent}
24.5			2.58
25	9.09		
26		6.12	
30	11.69		
30.5		6.89	3.64
32.3		7.29	
34	14.16		
34.5			4.35
34.8		8.68	
38.5			5.25
39	19.48		
41.6		11.46	
47.1		14.69	
48.5			8.43
49	32.47		
55	45.45		
58.5		23.98	
62.5			16.70

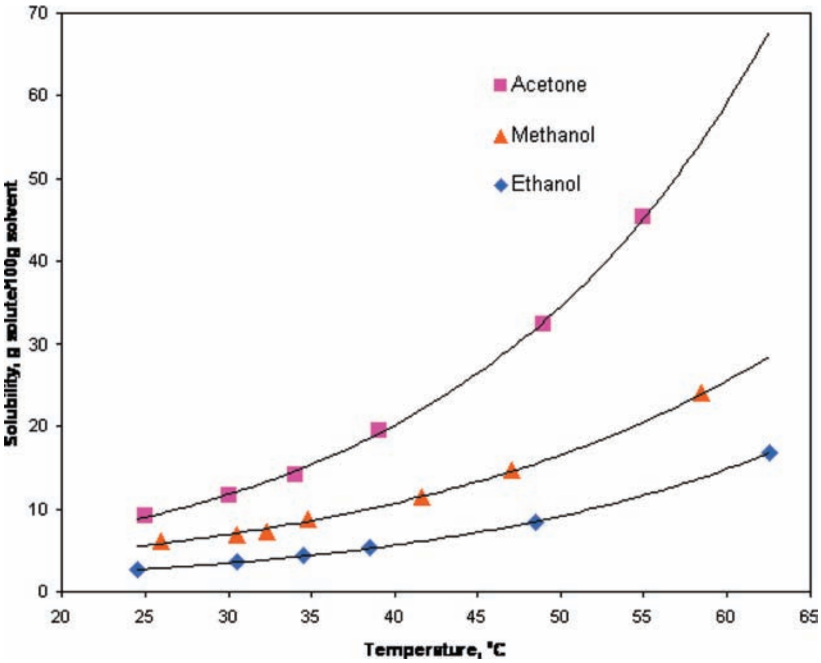

Figure 1. **Solubility curves of beclomethasone-17,21-dipropionate in selected organic solvents: acetone, methanol, and ethanol. The points are experimental data; the lines are the best fit of the data points.**

Table 4. **Volume, surface area, and adjustable parameters of the UNIQUAC model**

solvent	r	q	a_{12}[a]	a_{21}[a]
acetone	2.5735	2.3360	523.36	−116.51
mehanol	1.4311	1.4320	3069.2	832.2
ethanol	2.5755	2.5880	393.2	1340.90

[a] Subscript 1 refers to solvent and 2 refers to beclomethasone-17,21-dipropionate.

value. Then, by applying the estimated UNIQUAC activity coefficients, the adjustable parameters can be optimized. The optimization procedure is based on the minimization of the error between the calculated and experimental values of activity coefficient.

$$\text{min error}_{a_{12},a_{21}} = \sum_{k=1}^{n} (\gamma_{k,\text{exp.}} - \gamma_{k,\text{calc.}})^2 \qquad (15)$$

A Matlab program using *fmincon* function was written to optimize the adjustable parameters and evaluate the UNIQUAC activity coefficient, and consequently, the solubility of beclomethasone-17,21-dipropionate at various temperatures using the UNIQUAC equation.

Table 4 shows the optimized adjustable parameters of the UNIQUAC for the model system, beclomethasone-17,21-dipropionate in acetone, methanol, and ethanol.

The beclomethasone-17,21-dipropionate thermal properties, heat capacity (c_p), heat of fusion ($\Delta H_{\text{fus}}^{\text{m}}$), and the melting point (T_m) were determined using a differential scanning calorimeter (DSC, Mettler Toledo), (see Table 1). The mean values of heat of fusion ($\Delta H_{\text{fus}}^{\text{m}}$), and the melting point (T_m) are within ±0.35 J mol^{-1} and ±0.28 °C, respectively.

For beclomethasone-17,21-dipropionate, the volume and surface area parameters r_i and q_i were evaluated using eqs 11 and 12. A group contribution method was used to estimate the volume and surface area parameters on a functional groups basis.[17,18] The values of $\upsilon_k^{(i)}$, R and Q are given in Table 5. The final values of r_i and q_i parameters (eqs 11 and 12) are:

Table 5. **Functional groups and the group volume and surface area parameters of beclomethasone-17,21-dipropionate**

functional group	R	Q	$\upsilon_k^{(i)}$	$\upsilon_k^{(i)}R$	$\upsilon_k^{(i)}Q$
CH_3	0.9011	0.8480	5	4.5055	4.2400
$CH_2{=}CO$	1.4457	1.1800	2	2.8914	2.3600
CCl	1.0060	0.7240	1	1.0060	0.7240
OH	1.0000	1.2000	1	1.0000	1.2000
$CH_2{=}COO$	1.6764	1.4200	2	3.3528	2.8400
$CH{=}C$	0.8886	0.6760	1	0.8886	0.6760
C+C	0.6605	0.4850	1	0.6605	0.4850
CH_2	0.6744	0.5400	4	2.6976	2.1600
CH	0.4469	0.2280	4	1.7876	0.9120
C	0.2195	0.0000	2	0.4390	0.0000

$$r_i = 19.129$$

$$q_i = 15.597$$

Figure 2 shows the results of the thermodynamic modeling of beclomethasone-17,21-dipropionate in acetone, methanol, and ethanol. The UNIQUAC prediction provide good agreement with the experimental results. The best agreement was obtained with the experimental solubility data in acetone. Errors can occur in the solubility gravimetric measurements and also in the thermal analysis using DSC. An error of ± 10% in measuring

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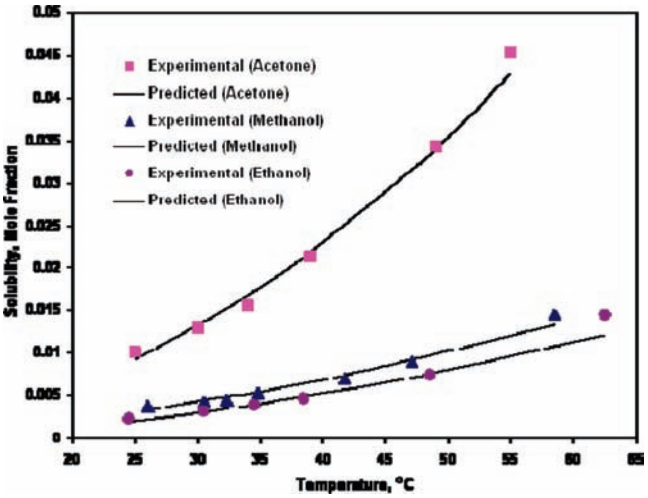

Figure 2. **Comparison of experimental to UNIQUAC model data for the solubility of beclomethasone-17,21-dipropionate in selected organic solvents; acetone, methanol and ethanol: The data points {■▲●} are experimental values determined by the visual/gravimetric technique, whereas the lines are UNIQUAC predicted data.**

Table 6. **Individual absolute relative deviations (IARD) between the experimental and UNIQUAC predicted solubility of beclomethasone-17,21-dipropionate in acetone, methanol and ethanol**

temperature, °C	IARD acetone	IARD methanol	IARD ethanol
24.5			2.8
25	3.0		
26		6.8	
30	1.0		
30.5		0.9	0.8
32.3		3.3	
34	4.4		
34.5			1.5
34.8		1.6	
38.5			3.4
39	2.2		
41.6		4.4	
47.1		2.3	
48.5			2.9
49	0.0		
55	11.3		
58.5		17.4	
62.5			36.8

the heat of fusion, and thus heat capacity and melting point, can result in a deviation up to 80% in the solubility prediction.

To provide reliable accuracy and to evaluate the UNIQUAC thermodynamic model capability, the individual absolute relative deviations (IARD) of constructed solubilities from experimental values were calculated by:

$$\mathrm{IARD} = 100\left(\frac{|x_i^{\mathrm{constructed}} - x_i^{\mathrm{experimental}}|}{x_i^{\mathrm{experimental}}}\right) \qquad (16)$$

Table 6 summarizes the results for all the solute−solvent systems. The individual absolute relative deviations between the experimental solubilities and the values obtained employing the UNIQUAC model are also indicated. The estimated average value of IARD was reasonably improved from 8% using ethanol to 3.7% employing acetone as a solvent. The estimated average value of IARD is found to be around 5.2% for methanol, a slight improvement from that of ethanol.

5. Conclusions

The equilibrium solubilities of beclomethasone-17,21-dipropionate in selected organic solvents, acetone, methanol, and ethanol over the temperature range of 24.5−62.5 °C were determined. Beclomethasone-17,21-dipropionate exhibited far higher solubility in acetone than in methanol. The solubility of solute in ethanol was low; consequently, acetone was chosen as the principle organic solvent to investigate the use of supercritical gas antisolvent crystallization for the micronization of beclomethasone-17,21-dipropionate.

The thermodynamically predicted solubility using the UNIQUAC model was in close agreement with the experimental gravimetric measurements. However, the best agreement was obtained with the experimental solubility of beclomethasone-17,21-dipropionate in acetone with an average individual absolute relative deviations value of 3.7%.

To the authors' knowledge, this is the first study of its kind to investigate solid−liquid equilibria (SLE) of beclomethasone dipropionate in organic solvents such as acetone, methanol, and ethanol and over a wide range of temperatures, empirically and theoretically.

NOTATION

c_p	heat capacity, J/g·°C
Δc_p	heat capacity difference between liquid and solid, J/g·°C
f_2^L	pure subcooled liquid fugacity of solute, Pa
f_2^S	pure solid fugacity of solute, Pa
ΔH_{fus}	heat of fusion, J/mol
P	pressure, Pa
q_i	surface area parameter for species i
r_i	volume parameter for species i
R	universal gas constant, J/mol·°C
T	temperature, K
T_m	melting point temperature, K
u_{ij}	a measure of the interaction energy for a species i−species j interaction
$\upsilon_k^{(i)}$	the number of groups of type k in molecule i
x_2	mole fraction of the solid solute, mol/mol
z	the average coordination number

GREEK LETTERS

γ_2	activity coefficient of the solid solute
φ_i	volume fraction of species i
θ_i	area fraction of species i

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