Calculating Critical Relative Humidity from Solubility According to Pitzer Ion Interaction Model

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The solubility and the critical relative humidity (H_{cr}) of 14 drugs and inorganic salts were determined, the relationship between the H_{cr} and the solubility was explored theoretically, and the H_{cr} was calculated in the light of Raoult's law and Pitzer ion interaction model from their solubility. The results indicate that the H_{cr} values calculated by Raoult's law in high humidity (H_{cr}>80%) and by Pitzer ion interaction model in low humidity (H_{cr}<80%) are comparable to the measured ones.

Key words critical relative humidity; solubility; Raoult's law; Pitzer ion interaction model

The critical relative humidity (H_{cr}) and the solubility are important physical properties that affect the quality of foodstuffs, drugs, fertilizers, chemicals and so on.[1—7] However, the H_{cr} is unclearly defined and there is little theoretical study reported.

For example, there are two definitions of H_{cr} in pharmaceutics: 1) A water-soluble drug powder is sensitive to humidity of surrounding air, above a certain relative humidity, it absorbs water significantly. The H_{cr} is defined as the relative humidity of atmosphere above which the drug powder starts to rapidly absorb water at a given temperature.[8,9] 2) There is equilibrium between gasiform water and liquid water in solution. The H_{cr} of a drug is the relative humidity of the surrounding air in equilibrium with the saturated solution of the drug at a given temperature.[9—11]

The H_{cr} of drugs can be regarded as a thermodynamic property based on definition 2. When disregarding minor factors, the H_{cr} is closely related to the interaction between drug and water molecules and that between drug molecules. The stronger the attraction between drug and water molecules is, the more difficult water molecules escape from the solution; therefore, the lower the relative humidity of atmosphere in equilibrium with the saturated solution (*i.e.* the H_{cr} of the drug) is. On the other hand, the stronger the attraction between drug molecules is, the relatively lower the attraction between drug and water molecules will be; therefore, the higher the H_{cr} of the drug is.

The above analogy can similarly be applied to the solubility of drugs in water. The stronger the attraction between drug and water molecules is, the higher the solubility is; the stronger the attraction between drug molecules is, the lower the solubility is. So we believe that the higher the solubility is, the lower the H_{cr} will be, and *vice versa*.[12]

This implies that there is a certain relationship between the H_{cr} and the solubility. The H_{cr} could be calculated from the solubility if we can find out this relationship. This would make it possible to obtain the H_{cr} which is difficult to be measured, by measuring the solubility which is relatively easy.

Wang *et al.*[12] calculated the H_{cr} of 21 electrolytes from the solubility according to Extended Non-random Two Liquid Model (NRTL) proposed by Sadeghi.[13] In this model, the activity coefficient of electrolytes in aqueous solution is represented by a sum of the contribution of a long-range and a short-range interaction term. In Wang's calculation, all the necessary energy parameters were from literatures.

An ion interaction model for electrolyte activity coefficients was developed by Pitzer[14—17] in the early 1970s which is based on hard-sphere model. Kim and and Frederick[18] obtained Pitzer ion interaction parameters from osmotic coefficient data on single electrolytes at high concentration, up to nearly saturation.

In our work, 14 drugs and inorganic salts served as a model. Their solubility was determined with titrimetry or UV spectrometry, and H_{cr} was determined by air humidity in equilibrium method. The measured H_{cr} was then compared with that calculated from the solubility in the light of Raoult's law in high humidity range and Pitzer ion interaction model in low humidity range respectively. The Pitzer ion interaction parameters we used were all from the literature.[18]

Experimental

Chemicals Nicotinamide (Biochemical Reagent (BR) >98.5%) was received from Shanghai Bio Life Science & Technology Co., Ltd. (China), Isoniazid (raw material, 99.0—101%) was received from Wuhan Yuancheng Technology Development Co., Ltd. Mannitol (Analytical Reagent (AR), >98.0%) was received from Tianjin Kermel Regent Chemicals Co., Ltd. (China) $ZnSO_4 \cdot 7H_2O$ (AR, >99.5%) was received from Sinopharm Chemical Reagent Co., Ltd. Citric acid (AR, >99.5%) and $Na_2S_2O_3 \cdot 5H_2O$ (AR, >99.0%) were received from Chengdu Fangzhou Chemical Regent Factory, $Mg(NO_3)_2 \cdot 6H_2O$ (AR, >99.0%) and Methenamine (AR, >99.0%) were received from Tianjin Regent Chemicals Co., Ltd. $MgCl_2 \cdot 6H_2O$ (AR, >98.0%), $Ca(NO_3)_2 \cdot 4H_2O$ (AR, >99.5%), and Calcium pantothenate (BR, >98.5%) were received from Chengdu KeLong Chemical Regent Factory, NH_4Cl (AR, >99.0%) was received from Tianjin Bodi Chemicals Holding Co., Ltd. $Zn(NO_3)_2 \cdot 6H_2O$ (AR, >99.0%) was received from Tianjin Jinhuitaiya Chemicals Reagent Holding Co., Ltd. (China).

Apparatus A pocket humidity meter (self-made, used to measure the H_{cr}),[19] an isothermal heating oven with high precision (self-made, the accuracy, precision, and reproducibility of temperature are ≤0.5 °C in the range of room temperature to 100 °C),[20] an electronic balance (FA2004, Liangping Shanghai Co., Ltd.) and a UV spectrophotometer (752C, from the third Analytical Apparatus Factory of Shanghai, used to determine the concentration of saturated nicotinamide solution.) were used.

In the humidity meter, a thermoset polymer integrated circuit humidity sensor (HIH-4010, Honeywell International Inc., U.S.A.) is used to linearly convert the relative humidity into voltage; a 3(1/2) digit A/D converter (ICL7106, Intersil Americas Inc., U.S.A.) is used to convert the humidity voltage analog to decimal digit, which is directly displayed as the H_r by a liquid crystal displayer.[19]

For the humidity meter, the H_r range is 0—100% with resolution 0.1%, respond time (1/e in the moving air) is 5 s. After calibrating with LiCl saturated solution (H_{cr}=11.3%) and NaCl saturated solution (H_{cr}=75.3%), the accuracy (25 °C, 0—95% H_r) is 2% and repeatability 1%.[19]

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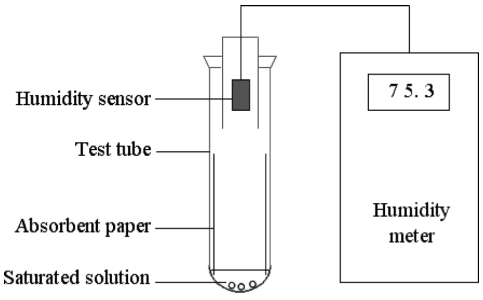

Fig. 1. Assembly Used in the H_{cr} Determination by Air Humidity in Equilibrium Method

Methods. Measuring H_{cr} by Air Humidity in Equilibrium Method About 2 ml of saturated sample solution with a little crystal was placed in a sealed test tube. A piece of absorbent paper was put into the test tube in order to increase the evaporating area. The humidity sensor was sealed at the headspace of the test tube as shown in Fig. 1. Then the test tube was put in the thermostatic oven that could maintain the temperature to 25 °C. After 1 h incubation (although the respond time of the humidity sensor is about 5 s, 20—30 min are needed for the gas–liquid equilibrium), the relative air humidity in the test tube, *i.e.* the H_{cr} of the sample, was measured with the humidity meter.[19)]

Measuring Solubility A certain amount of water and excess drug were placed into a beaker. To reach saturation, stirring is promoted for 48 h at 25 °C, controlled by an isothermal heating oven. The mixing was then stopped and the solution was allowed to settle at least 4 h before sampling with a preheated pipette. The sample was withdrawn from the supernatant phase and was filtered with 0.45 μm microporous filtering film and the filtrate was then taken for titration or UV spectrophotometric determination according to the physicochemical property of different drugs.

The saturated solution of mannitol was titrated at 25 °C with $Na_2S_2O_3$ solution; that of citric acid and methenamine were titrated with NaOH solution; isoniazid was titrated with $KBrO_3$ solution; NH_4Cl was titrated with $AgNO_3$ solution; calcium pantothenate, $CaCl_2\cdot 2H_2O$, $MgCl_2\cdot 6H_2O$, $Ca(NO_3)_2\cdot 4H_2O$, $Zn(NO_3)_2\cdot 6H_2O$ and $ZnSO_4\cdot 7H_2O$ were titrated with ethylene diamine tetraacetic acid (EDTA)-2Na solution. The solubility of nicotinamide was determined with UV spectrophotometry at wavelength 261 nm.

Results and Discussion

Calculating H_{cr} from Solubility According to Raoult's Law According to Raoult's law, in an aqueous solution, the vapor pressure of water in equilibrium with the solution is proportional to the mole fraction of water and can be expressed as:

$$p_A = p_A^* x_A \quad \text{or} \quad \frac{p_A}{p_A^*} = x_A \tag{1}$$

where p_A is the vapor pressure of water, p_A^* is the vapor pressure of pure water, x_A is the mole fraction of water and is also the relative humidity (p_A/p_A^*) of the atmosphere in equilibrium with the solution. When the solution is saturated, $x_{A,sat}$ (the subscript "sat" denotes saturated state) is just the H_{cr} of the solute:

$$H_{cr}=p_A/p_A^*=x_{A,sat} \tag{2}$$

The $x_{A,sat}$ is:

$$x_{A,sat}=(100/M_A)/[(100/M_A)+(\nu S/M_B)] \tag{3}$$

where M_A and M_B are the molecular weight of water and the solute respectively, S is the solubility. For aqua compounds, M_B and S were treated as anhydrous substance.

For a strong electrolyte $M_{\nu+}A_{\nu-}$, ν_+, ν_-, and ν ($\nu=\nu_++\nu_-$) are the stoichiometric coefficient of cation, anion, and total ions in a molecule; for a non electrolyte ν is 1; and for a weak electrolyte ν is close to 1 and was treated as 1 in our calculation.

Table 1. The Calculated and Measured H_{cr}

Drugs and electrolytes	S (g/100 g water)	H_{cr} (%)		
		Measured	Calculated according to	
			Raoult's law	Pitzer model
Mannitol	17.53±0.06	97.9±0.404	98.30±0.035	—
Citric acid	154.35±1.02	81.2±0.500	87.36±0.073	—
Methenamine	95.40±1.18	83.2±0.321	89.07±0.121	—
Isoniazid	14.14±0.12	92.3±0.737	98.18±0.019	—
Nicotinamide	90.63±0.85	96.6±0.379	88.21±0.120	—
Calcium pantothenate	80.50±0.27	93.2±0.551	91.64±0.032	—
$ZnSO_4\cdot 7H_2O$	56.39±0.21	87.0±0.208	88.80±0.037	79.31±0.12
$CaCl_2\cdot 2H_2O$	77.60±0.33	27.8±0.751	72.59±0.083	25.64±0.255
$MgCl_2\cdot 6H_2O$	59.92±0.35	33.8±0.608	74.91±0.111	26.03±0.389
$Zn(NO_3)_2\cdot 6H_2O$	121.19±0.85	42.3±0.551	74.28±0.133	37.09±0.386
NH_4Cl	38.75±0.07	79.5±0.404	79.32±0.033	77.54±0.040
$Ca(NO_3)_2\cdot 4H_2O$	129.73±1.47	50.4±0.721	70.07±0.237	48.25±0.435
$Na_2S_2O_3\cdot 5H_2O$	76.15±0.78	76.1±0.850	79.35±0.169	70.30±0.405
$Mg(NO_3)_2\cdot 6H_2O$	72.21±0.63	55.9±0.569	79.15±0.144	49.76±0.478

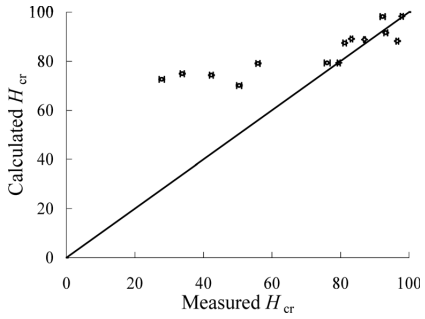

Fig. 2. The Comparison of the H_{cr} Calculated by Raoult's Law and the Measured One

The mole fraction of water in the saturated solution, *i.e.* the H_{cr}, was calculated according to Raoult's law, and was compared with the measured one. The result is listed in Table 1 (column 3 and 4) and plotted in Fig. 2.

The straight line in Fig. 2 is a reference line in which the calculated H_{cr} is equal to the measured one. Actually, it is seen from Fig. 2 that the points are approximately in the straight line in high H_{cr} range (>80%) and above the line in low H_{cr} range (<80%), which indicates the saturated solutions disobey Raoult's law when the H_{cr} of the drugs is lower than 80%.

It is simply because Raoult's law is a limiting law applied to ideal solution or diluted solutions. A saturated solution is usually a non-ideal solution and there are various complex interactions among the particles in the solution and therefore we can not expect Raoult's law well accord with a real solution in high concentration range.

Calculating H_{cr} from Solubility According to Pitzer Ion Interaction Model Raoult's law can not well accord with solutions in high concentration range because of the neglect of the activity coefficient of water which is closely related to the interactions among the particles. In a real solution the activity of water should be used instead of the mole fraction of water, Raoult's law can be expressed as:

$$p_A = p_A^* a_A = p_A^* x_A \gamma_A \quad (4)$$

where a_A is the activity of water, γ_A is the activity coefficient of water. Combining Eq. 4 with the Eq. 2 yields:

$$H_{cr} = \frac{p_{A,sat}^* a_{A,sat}}{p_A^*} = a_{A,sat} = \gamma_{A,sat} x_{A,sat} \quad (5)$$

Equation 5 indicates the activity of water in the saturated solution is just the H_{cr} of the drug.

In an ideal solution, the value of γ_A is 1, so the activity of water is the mole fraction of water. In a real solution, the value of γ_A is related to the concentration of the solution; however, it changes insignificantly in a rather wide concentration range and is very close to 1. To enlarge the difference between the ideal solution and real solutions, osmotic coefficient ϕ is often used instead of γ_A for water. The value of ϕ changes much significantly than that of γ_A.

The osmotic coefficient ϕ can be expressed as[21]:

$$\phi = -\frac{\ln a_A}{M_A \nu m} \quad (6)$$

where m is the total molality.

Based on Pitzer model, Harvie and Weare raised an equation to calculate the ϕ for single electrolyte solutions. At 25 °C,

$$\phi = 1 + \frac{2}{(m_+ + m_-)} \left\{ \frac{-0.392 I^{0.5}}{1 + 1.2 I^{0.5}} + m_+ m_- \left(\beta_{MX}^{(0)} + \beta_{MX}^{(1)} \exp(-2 I^{0.5}) + 2 \left(\sum_+ m_+ |z_+| \right) C_{MX}^{\phi} \Big/ 2 |z_+ z_-|^{0.5} \right) \right\}$$

(for electrolytes other than 2-2 type) (7a)

or

$$\phi = 1 + \frac{2}{(m_+ + m_-)} \left\{ \frac{-0.392 I^{0.5}}{1 + 1.2 I^{0.5}} + m_+ m_- \left(\beta_{MX}^{(0)} + \beta_{MX}^{(1)} \exp(-1.4 I^{0.5}) + \beta_{MX}^{(2)} \exp(-12 I^{0.5}) + 2 \left(\sum_+ m_+ |z_+| \right) C_{MX}^{\phi} \Big/ 2 |z_+ z_-|^{0.5} \right) \right\}$$

(for 2-2 type electrolyte) (7b)

where m_+ is the molality of a cation with charge z_+ corresponding to stoichiometric coefficient ν_+. Similarly, the subscript "−" refers to an anion. I is the ionic strength,

$$I = \frac{1}{2} \sum_i m_i z_i^2$$

The parameters $\beta_{MX}^{(0)}$, $\beta_{MX}^{(1)}$, $\beta_{MX}^{(2)}$ and C_{MX}^{ϕ} for some drugs we used were reported by Kim and Frederick.[18]

After calculating the ϕ according to Eq. 7, the activity of water in the saturated solution (*i.e.*, the H_{cr}) can be obtained by Eq. 8 which is rearranged from Eq. 6:

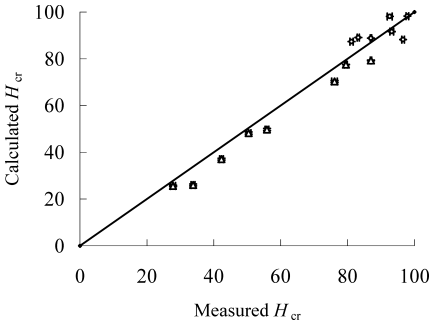

Fig. 3. The Comparison of the Calculated and Measured H_{cr}
△, calculated by Pitzer model; ○, calculated by Rault's law.

$$a_A = \exp(-\phi M_A \nu m) \quad (8)$$

The result is listed in Table 1 (column 4 and 5) and plotted in Fig. 3. It is seen from Fig. 3 that the data points calculated by Pitzer model are close to the straight line in low H_{cr} range (<80%).

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