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ORIGINAL ARTICLE

Relationship between critical relative humidity and solubility of drugs

Yingli Wang, Xiancheng Zhan, Lin Luo, Jia Chen, Chaoqun Xiang, Chengrong Li, and Linli Li

Key Laboratory of Drug Targeting, West China School of Pharmacy, Sichuan University, Chengdu, Sichuan 610041, P. R. China

Abstract

Both the critical relative humidity (H_{cr}) and the solubility are important physicochemical properties that affect the quality of drugs. However, the relationship between them is not noticed yet. By an analysis of interaction between molecules of drug and water, the conclusion logically obtained is: the higher the solubility is, the lower the H_{cr} will be. To validate this idea, the H_{cr} and the solubility of 33 drugs and chemicals were determined and a negative linear correlation was found between the two factors when the solubility was expressed as the mole fraction of water. This negative linear correlation was further confirmed by a computer simulation according to modified Debye-Hückel equation.

Keywords: Critical relative humidity; air humidity in equilibrium method; solubility; computer simulation; Debye-Hückel equation

Introduction

Both the critical relative humidity (H_{cr}) and the solubility in water are important physicochemical properties that affect the quality of drugs, foodstuffs, fertilizers, chemicals, and so on (Young, 1967; Labuza et al., 1976; Greespan, 1977; Byrn et al., 2001). 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 the relative humidity of surrounding air, above a certain level, and will absorb water. 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 (Cui, 2003). (2) There is equilibrium between gasiform water and liquid water in a solution. The H_{cr} of a drug is the relative humidity of the surrounding air in equilibrium with the saturated solution at a given temperature (Wang et al., 1989). Definition 2 is in agreement with thermodynamic principle: when the relative humidity in the air in equilibrium with the saturated solution is above the H_{cr}, the solution will absorb water and gain weight; when it is below H_{cr}, the solution will lose water and weight; and when just equal to it, the solution will neither absorb nor lose water and keep its weight constant.

Accordingly, there are two conventional methods to determine the H_{cr}: (1) the powder moisture adsorption method (Cui, 2003) and (2) the saturated solution method (Wang et al., 1989). The former is based on definition 1 and the latter is based on definition 2. Later on, an instrumentation method, dynamic vapor sorption method, was used as an improvement of traditional methods (Wadsö et al., 2009). In these methods, H_{cr} was measured by measuring the weight change indirectly. Recently, a new method called air humidity in equilibrium method was proposed (Zhan et al., 2010). In this method, the H_{cr} is determined by measuring the relative air humidity in equilibrium with saturated solution of drugs directly.

The H_{cr} of a drug can be regarded as a thermodynamic property based on the definition 2. When disregarding minor factors, the H_{cr} is closely related to the interaction between molecules of the drug and water, and the interaction between drug molecules. The stronger the attraction between drug and water molecules is, the more difficult

Address for Correspondence: Xiancheng Zhan, Key Laboratory of Drug Targeting, West China School of Pharmacy, Sichuan University, Chengdu, Sichuan $610041, P. R. China. Tel.: +8613618091154. E-mail: xczhan@mail.sc.cninfo.net

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for the water molecules to escape from the solution, and therefore 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, and therefore higher the H_{cr} of the drug is.

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

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 might make it possible to obtain the H_{cr}, which is usually difficult to measure, by measuring the solubility easily. On the contrary, using the newly proposed measuring method (Zhan et al., 2010), the H_{cr} measurement is even easier than the solubility measurement. So for some drugs (such as saccharides) whose solubility is difficult to measure, we might calculate their solubility from their H_{cr}.

To validate the above idea, the H_{cr} and the solubility of 33 drugs and chemicals were determined and a linear relationship was found between the two factors when the solubility was expressed as mole fraction of water.

To explain the relationship theoretically, a computer simulation was carried out according to modified Debye-Hückel equation $\ln\gamma_{\pm,\mathrm{m}} = -\frac{1.1709|z_+ z_-|I^{0.5}}{1+aI^{0.5}} + bI$. The results from the computer simulation are approximately comparable with those from real experiment.

Experimental

Instruments

A pocket humidity meter (self-made) (Zhan et al., 2010) was used to measure the relative air humidity. In the humidity meter, a thermoset polymer-integrated circuit humidity sensor (HIH-4010, Honeywell International Inc., USA) is used to linearly convert the relative humidity into voltage, a $3\frac{1}{2}$ digit A/D converter (ICL7106) is used to convert the humidity voltage analog to decimal digit, which is directly displayed as the relative humidity (H_r) by a liquid crystal displayer.

For the humidity meter, the relative humidity range is 0–100% H_r with resolution 0.1% H_r, respond time (1/e in the moving air) is 5 sec. 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 0.5%.

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) (Zhan et al., 1995) and an electronic balance (FA2004, Liangping Shanghai Co.) were used.

Drugs and chemicals

All drugs and chemicals used were analytical or officinal reagent.

Measuring H_{cr} by air humidity in equilibrium method

On the basis of the definition 2, to measure the H_{cr} of a drug, we can simply measure the relative air humidity in equilibrium with the saturated solution of the drug. About 2 ml of saturated sample solution with a little crystal was placed in a sealed cuvette. A piece of absorbent paper was put into the cuvette to increase the evaporating area. The humidity sensor was sealed at the headspace of the cuvette as shown in Figure 1. Then, the cuvette 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 cuvette, that is, the H_{cr} of the sample, was measured with the humidity meter. The measured H_{cr} of 33 drugs is listed in Table 1 (Zhan et al., 2010).

Determination of 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 gravimetric analysis according to the physicochemical property of different drugs. The solubility (expressed as g/100 g water) is listed in Table 1.

Determination of solubility with titrimetry

An appropriate amount of saturated solution was accurately weighted and was transferred into a volumetric flask, and water was added to volume. Then, an appropriate amount of the diluent was titrated with proper titrant. The solubility was calculated according to the mass of solution and solute and is listed in Table 1 (Pharmacopoeia of China, 2005).

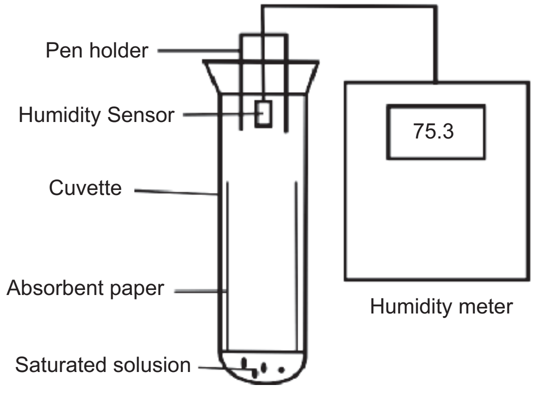

Figure 1. Assembly used in H_{cr} determination by air humidity in equilibrium method.

Determination of solubility with gravimetry

An appropriate amount of saturated solution was accurately weighted into a weighing bottle. The next step was to evaporate all water in the sample, and to dry completely the crystals in a drying stove at 105°C. Finally, the sample was cooled in a dehydrator with gel and then weighed. The process was regularly repeated until a constant mass value was achieved. Then, the solubility was calculated according to the mass of solution and solute (Ferreira et al., 2007).

Results and discussions

To study the relationship between the H_{cr} and the solubility, we first obtained a linear regression line from the data in Table 1 with a rather low correlation coefficient ($r = -0.7750$, shown in Figure 2) by plotting the H_{cr} versus the solubility expressed as g/100g.

On the basis of the colligative property, the vapor pressure of dilute solution depends on the number of solute particles rather than on their chemical nature. So, we then obtained a linear regression line from the data in Table 1 with a better correlation coefficient ($r = -0.9290$, Figure 3) by plotting H_{cr} versus solubility expressed as species molality (the total number of moles of ions or molecules per kilogram of water in the solution).

According to Raoult's law, in ideal solution or dilute solution, the vapor pressure of water in equilibrium with the solution is proportional to the mole fraction of water and can be expressed as:

$$p_A = p_A x_A \ or \ p_A/p_A^* = x_A \quad (1)$$

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 ($H_r = p_A/p_A^*$) of the atmosphere in equilibrium with the solution. When the solution is saturated (presuming that the solutions still accord to Raoult's law), $x_{A,\,sat}$ (the subscript "sat" denotes saturated state) is just the H_{cr} of the sample:

Table 1. Solubility and H_{cr} of selected 33 drugs.

	ν	H_{cr}[a]	Solubility (g/100g)[a]	Species molality (mol/kg)	x_A
Sodium oxalate	3	0.992 ± 0.008	3.70 ± 0.19[b]	0.8286	0.9852
Sodium dodecylsulfate	2	0.991 ± 0.008	4.67 ± 0.34[b]	0.3426	0.9938
EDTA-Na_2	3	0.986 ± 0.004	10.09 ± 0.74[c]	0.9000	0.9840
Zinc gluconate	3	0.979 ± 0.008	13.44 ± 0.34[c]	0.8850	0.9843
Barbital sodium	2	0.939 ± 0.009	20.42 ± 0.89[b]	1.981	0.9655
Sodium tartrate	3	0.936 ± 0.011	30.72 ± 0.54[b]	4.749	0.9211
Sodium succinate	3	0.893 ± 0.012	35.51 ± 0.93[b]	6.573	0.8941
Potassium oxalate	3	0.877 ± 0.011	36.57 ± 0.92[b]	6.600	0.8937
Sodium acetate	2	0.758 ± 0.002	51.8 ± 1.01[b]	12.64	0.8144
Sodium citrate	4	0.888 ± 0.002	55.98 ± 1.10[b]	8.676	0.8648
Sodium benzoate	2	0.893 ± 0.008	57.47 ± 0.95[b]	7.976	0.8743
Magnesium acetate	3	0.758 ± 0.009	65.14 ± 0.93[c]	13.72	0.8017
Sodium salicylate	2	0.826 ± 0.005	111.21 ± 0.95[b]	13.80	0.8007
Potassium sorbate	2	0.708 ± 0.010	140.33 ± 0.83[b]	18.68	0.7481
Potassium citrate	4	0.631 ± 0.002	158.46 ± 1.34[b]	20.69	0.7284
potassium acetate	2	0.234 ± 0.013	273.12 ± 1.87[b]	55.66	0.4992
Sorbitol	1	0.768 ± 0.011	233.80 ± 4.9[c]	12.83	0.8123
Mannitol	1	0.979 ± 0.004	17.53 ± 0.06[c]	0.962	0.9829
Citric acid monohydrate	1	0.812 ± 0.005	154.35 ± 1.01[c]	8.033	0.8736
Methenamine	1	0.832 ± 0.003	95.4 ± 1.66[c]	6.805	0.8908
Isoniazid	1	0.926 ± 0.013	14.40 ± 0.12[c]	1.031	0.9817
Niacinamide	1	0.966 ± 0.004	90.63 ± 0.85[b]	7.421	0.8821
Calcium pantothenate	3	0.934 ± 0.016	80.50 ± 0.27[c]	5.068	0.9426
Calcium nitrate tetrahydrate	3	0.504 ± 0.007	129.73 ± 1.47[c]	23.72	0.7006
Zinc sulphate heptahydrate	2	0.870 ± 0.002	56.39 ± 0.21[c]	6.985	0.8880
Ammonium Chloride	2	0.795 ± 0.004	38.75 ± 0.11[c]	14.49	0.7931
Sodium thiosulfate	3	0.761 ± 0.008	76.15 ± 0.78[c]	14.45	0.6979
Magnesium nitrate	3	0.554 ± 0.006	72.21 ± 0.63[c]	14.61	0.7089
Calcium lactate	3	0.985 ± 0.012	4.054 ± 0.05[c]	0.394	0.9929
Ethylamine sulfonic acid	1	0.988 ± 0.011	10.07 ± 0.07[c]	0.8046	0.9857
Choline theophyllinate	2	0.678 ± 0.001	116.7 ± 0.35[c]	8.244	0.8706
Meglumine	1	0.911 ± 0.025	90.62 ± 0.23[c]	4.643	0.9227
Tranexamic acid	1	0.981 ± 0.003	13.61 ± 0. 02[c]	0.8657	0.9846

ν: The number of total ions in a molecule. [a]Mean ± S.D. of three measurements; [b]measured by gravimetry; [c]measured by titrimitry.

$$H_{cr} = p_{A,sat}/p_A^* = x_{A,sat} \qquad (2)$$

Finally, according to Equation (2), a straight line $H_{cr} = 1.3735x_{A,sat} - 0.3588$ was obtained by plotting the H_{cr} versus the solubility expressed as mole fraction of water from the data in Table 1 and is shown in Figure 4. The correlation coefficient ($r = 0.9345$) is higher than those of above two. From the straight line, when $x_{A,sat} = 1$, the H_{cr} is 1.0147, which is very close to the theoretical value 1.

To explain the relationship between the H_{cr} and the solubility theoretically, computer simulations were carried out. In real solutions, the activity of water should be used (Wang et al., 2009) instead of mole fraction of water, then the vapor pressure of water can be expressed as $p_A = p_A^* a_A$, and H_{cr} can be expressed as:

$$H_{cr} = p_A^* a_{A,sat} / p_A^* = a_{A,sat} = x_{A,sat}\gamma_{A,sat} \qquad (3)$$

where $a_{A,sat}$ is the activity of water and $\gamma_{A,sat}$ is the activity coefficient of water in saturated solutions.

There are some models that can be used to calculate the activity coefficient, such as modified Debye-Hückel model (Debye & Hückel, 1923), Pitzer model (Pitzer, 1973; Pitzer and Mayorga, 1973), extended Wilson model (Zhao et al., 2000), extended nonrandom two-liquid model (Sadeghi, 2006), and extended universal quasichemical model (Messnaoui et al., 2008) and so on.

In modified Debye-Hückel model, the mean activity coefficient $\gamma_\pm$ of solutes is independent of the chemical property of specific ions and is expressed as Equation (4) in dilute solution:

$$\ln\gamma_{\pm,m} = -\frac{1.1709\,|z_+z_-|\,I^{0.5}}{1+aI^{0.5}} + bI \qquad (4)$$

where $\gamma_{\pm,m}$ is the mean ionic activity coefficient, I is ionic strength in molality scale, a is a parameter related to ionic size, and b is an empirical term.

In our computer simulations, the activity coefficient of electrolyte $\gamma_\pm$ was calculated according to Equation (4) with $a = 1$ and $b = 0.015$. Then, the activity coefficient of water was calculated according to Gibbs-Duhem equation in isothermal and isopiestic conditions. $x_A d\ln\gamma_A + x_+ d\ln\gamma_{+,x} + x_- d\ln\gamma_{-,x} = 0$. Finally, the H_{cr} was obtained from Equation (3) and is shown in Figure 5. It is seen from Figure 5, the results of the computer simulations are approximately comparable with those of the real experiments (see Figure 4).

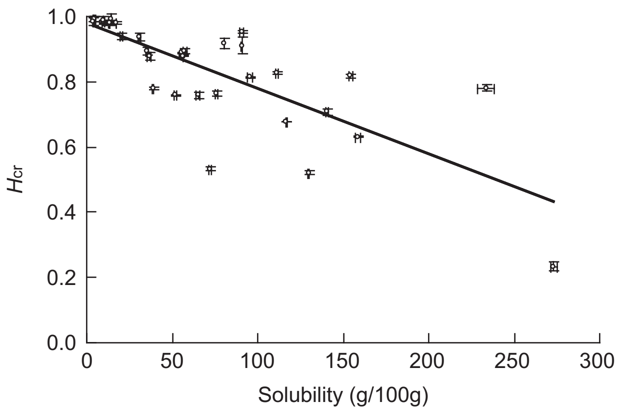

Figure 2. The relationship between H_{cr} and solubility expressed as g/100 g.

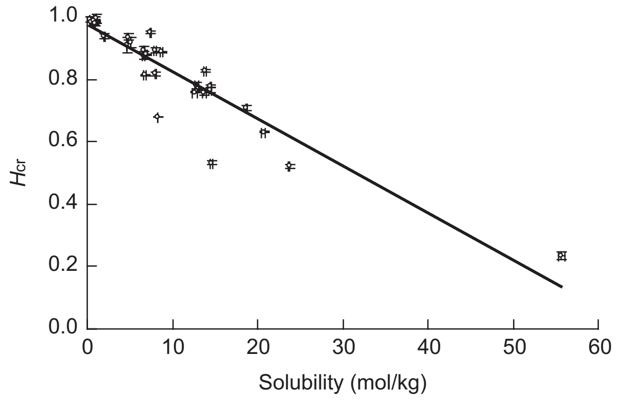

Figure 3. The relationship between H_{cr} and solubility expressed as species molality.

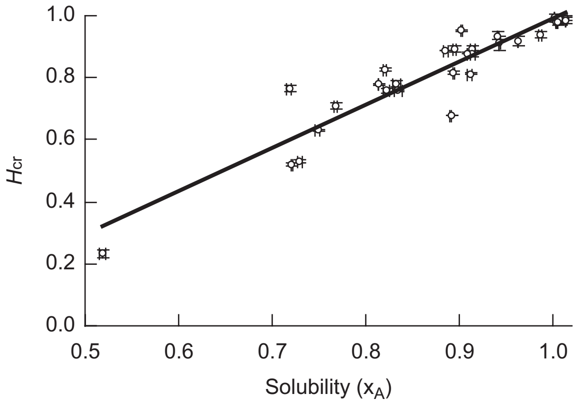

Figure 4. The relationship between H_{cr} and solubility expressed as mole fraction of water.

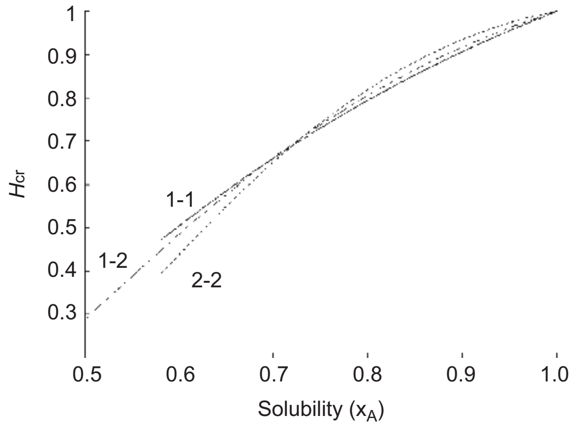

Figure 5. Relationship between H_{cr} and x_A in computer simulation according to Equation (4) with $a = 1$, $b = 0.015$ for electrolyte type 1-1, 1-2, and 2-2.

Conclusion

In conclusion, there is a negative linear correlation between the H_{cr} and the solubility expressed as mole fraction of water, and the H_{cr} can be estimated from the empirical equation $H_{cr} = 1.3891x_A - 0.3728$ approximately.

Declaration of interest

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