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Research Paper

Impact of the Amount of Excess Solids on Apparent Solubility

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Purpose. The impact of excess solids on the apparent solubility is examined.
Methods. The apparent solubility of some model drugs was measured in various buffered solutions, with various amounts of excess solid. To help understand the dependence of the solubility on the amount of solid, we evaluated the dissolution and crystallization rates of indomethacin (IDM), one of the model drugs, at near-equilibrium conditions.
Results. In the case of IDM, the apparent solubility decreased with an increase in the solid amount at pH 5 and 6. On the other hand, it increased with an increase in the solid amount at pH 6.5 and 7. The crystallization and dissolution rates of IDM decreased and increased, respectively, with an increase in pH values, and became equal at between pH 6 and 7. Therefore, the apparent solubility was most likely to be affected by the balance between the crystallization and dissolution rates. The apparent solubility of other model drugs showed the same trend, although the dependency on the solid amount was not as significant as in the case of IDM.
Conclusions. The apparent solubility was affected by the amount of solid for all the model drugs investigated. This was most likely to be caused by a competition between the crystallization and dissolution rates.

KEY WORDS: crystallization; dissolution; excess solids; solubility.

INTRODUCTION

Aqueous solubility is one of the most important characteristics of pharmaceutical solids in developmental research, because it frequently has a direct effect on bioavailability. Therefore, many methodologies (1,2), including *in silico* predictions (3), have been developed to quickly assess aqueous solubility. In the later stages of development, more precise determination of the aqueous solubility is necessary for designing appropriate formulations. However, precise equilibrium solubility values are very difficult to obtain, because they are affected by many factors, both known and unknown (4). Table I shows some examples of reported aqueous solubility values (5). As can clearly be seen, variations of the solubility among reports are very large with the discrepancy sometimes being as large as 25-fold. One of the most likely explanations for this may be the effect of particle size. Assuming that a particle is spherical, the Kelvin equation (4,6) can be applied.

$$C(r) = C(\infty) \exp\left(\frac{2\gamma M}{r\rho RT}\right) \quad (1)$$

where $C(r)$ and $C(\infty)$ are the solubilities of a particle of radius r and of infinite size. γ, M, and ρ are interfacial tension at the particle surface, the molecular weight of the solute, and the density of the particle, respectively. R and T have their usual meanings. This equation shows that the solubility decreases monotonically with an increase in droplet size. Because the solubility of small particles is higher than that of larger ones, the small particles are preferentially dissolved. This solubility corresponds to "oversaturation" for larger particles. Thus, they grow by adsorbing the solutes onto their surfaces. This phenomenon is the so-called Ostwald ripening. Therefore, although the true equilibrium solubility should be $C(\infty)$, an apparent higher solubility can be observed if the small particles are present in a system. The micronization of drugs to improve their dissolution behavior (7) is partially based on this principle.

Another factor of concern may be the crystallinity. Because of the higher chemical potential of amorphous solids and the thermodynamic relationship of $\mu_i = \mu^* + RT \ln x_i$, where μ_i, μ^*, and x_i are the chemical potential of i (i = amorphous or crystal), that in a reference state, and the mole fraction of the compound, respectively, the solubility of the amorphous part is higher than that of the crystal part. When the amorphous is dissolved in a solvent, the most typical observation is an initial high solubility, followed by its decrease due to gradual crystallization. However, it should also be noted that the amorphous solid is prone to display oversaturation even without this crystallization behavior.

The time to the attainment of an equilibrium state is also a very important issue, although not much has been discussed in literature. Several days or weeks are the typical choice in a careful experiment to attain the equilibrium state. However, shorter periods need to be selected frequently due to the chemical instability of compounds or insufficient information

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Table I. Variation of Aqueous Solubility in Literature (25°C)

Compound	Solubility range (g/ml)
Estradiol	0.16–5.00
Indomethacin	4.00–14.0
Griseofulvin	8.00–13.0
Progesterone	7.90–200
Digoxin	28.0–97.9
Riboflavine	66.0–99.9
Dexamethasone	89.1–121.0
Hydrocortisone	280–359

on this subject. Therefore, variations in the experimental period may also become a reason for discrepancy in the solubility data.

What will be described in this paper is the effect of the amount of excess solids on the apparent solubility. Little has been reported in the literature on the amount of solid added, indicating poor attention to this matter. One curious example of focus on the amount of excess solid was reported recently (8), where an excess of di-HCl salt compound affected the solubility of the mono-HCl salt due to a common ion effect. Therefore, this observation is specific to salt forms. Here we describe the effect of excess solid on the apparent solubility of free acids and a base at various pH conditions.

MATERIALS AND METHODS

Materials

Indomethacin (IDM), phenytoin (PHT), and pindolol (PDL) were obtained from Wako Pure Chemicals (Osaka, Japan). Crystal forms of IDM and PHT were confirmed to be the most stable form using powder X-ray diffraction and differential scanning calorimetry (DSC) (9–12). Tolbutamide (TLB), which was also of the most stable form, was purchased from Sigma-Aldrich (St. Louise, MO, USA). Although TLB exhibits enantiotropic transition at 40°C, the most stable forms are always obtained under ambient conditions due to their totally reversible character (12). All reagents were of the highest grade available and used as supplied.

Solubility Measurement

The desired amount of the compound was placed in a test tube, to which an appropriate amount of solvent was introduced. The buffer types used were citrate (pH 3–5), phosphate (pH 6–8), and carbonate (pH 9, 10). The pH values were not affected after introducing model drugs in all the cases. The test tubes were rotated at 50 rpm for the desired duration, followed by filtration using syringe filters of 450-nm pore size in a temperature-controlled room at 37°C. All the glassware and filters used for this filtration were prewarmed in the room for at least 1 h to avoid precipitation during the filtration. The filtrates were diluted with a 1:1 mixture of acetonitrile/water and subjected to HPLC analysis. Concentration of IDM and PDL was determined using YMC pack ODS-AM-3C2 [150 mm (L) × 2.0 mm (ID); YMC Co., Kyoto, Japan) with a flow rate at 0.2 ml/min. In the IDM experiments, the mobile phase, detection wavelength, and injection volume were 0.1 vol.% trifluoroacetic acid (TFA)/acetonitrile = 50:50, 260 nm, and 2 μl, respectively. In the case of PDL, the solvent ratio and the detection wavelength were 85:15 and 264 nm, respectively. For other compounds, Symmetry Shield Rp-18 [50 mm (L) × 4.6 mm (ID); Waters Corp., Milford, MA, USA] was used as a separation column with a flow rate of 2 ml/min. The solvent ratio was linearly changed from 0.1% TFA/acetonitrile = 85:15 to 10:90 in 6 min. The detection wavelength and the injection volume were 238 nm and 8 μl, respectively, for both compounds.

Dissolution Rate Near Equilibrium Condition

Because the dissolution rate decreases with the lapse of time even at constant undersaturation (13,14), a "normal" dissolution test is not adequate for evaluating the dissolution behavior near the equilibrium condition. Therefore, the equilibrated dispersions were first prepared by dispersing the desired amount of IDM in the buffered solutions 2 days prior to the experiments. In the experiment, the dispersions were diluted using the same buffers at the desired dilution rate. The details of the experimental conditions are shown in Table II. The dispersions were subjected to the quantification of IDM as described above. All the procedures were performed in a temperature-controlled room at 37°C.

Crystallization Rate Near Equilibrium Condition

Preliminary studies revealed that the injection of dimethylsulfoxide (DMSO) solutions of IDM into buffered solutions of pH 5, 6, and 7 at 37°C yielded the α-form (9,10). However, in the presence of excess solids of the γ-form, the resultant crystal form was of the γ-type. A powder X-ray diffraction experiment confirmed that the amount of the α-form was below the detectable level, even after IDM was added as a DMSO solution in an amount larger than the γ-form solids. Therefore, the equilibrated dispersions were prepared beforehand by dispersing the desired amount of γ-form IDM in the buffered solutions 2 days prior to the experiments. To these saturated dispersions, the DMSO solution of IDM was slowly added using Hamilton syringes. The final DMSO concentration in the dispersions was 2% at maximum, where the effect on the IDM solubility was not significant (15). Details of the experimental conditions are presented in Table III. The glass vials containing the dispersions were rotated at 50 rpm for the desired period. The

Table II. Experimental Conditions for the Dissolution Study

PH	Initial C_t (mg/ml)	Dilution rate	Final C_t (mg/ml)	C_i (mg/ml)	C_f (mg/ml)
5	0.4	2	0.2	0.0092	0.020
	0.6	3	0.2	0.0056	0.020
	0.8	4	0.2	0.0041	0.020
6	2	2	1	0.059	0.12
	3	3	1	0.038	0.12
	4	4	1	0.028	0.12
7	20	2	10	0.58	1.10
	29	3	10	0.41	1.10
	40	4	10	0.32	1.10

C_t: Total drug amount in the system (i.e., solute + precipitation), C_i: initial solute concentration, C_f: final solute concentration.

dispersions were subjected to the quantification of IDM as described above. All the procedures were performed in a temperature-controlled room at 37°C.

RESULTS AND DISCUSSION

Preliminary Study: Case of IDM

Prior to the solubility measurement, the particle size of IDM was measured using a particle size analyzer (GALAI WCIS-50 Particle Analyzer: Ankersmid Ltd., Yokneam, Israel), because this is also an important factor affecting the solubility (4,6). The measurements were repeated from 1 h to 5 days after dispersing IDM in the buffered solutions. At all pH conditions, the measured mean diameters were between 20 and 30 μm without any tendency of increasing or decreasing, suggesting that the particle size did not change during the 5 days.

In addition, if the particle size is large enough, the particle surface can be regarded as flat. An example of a model calculation regarding the dependence of solubility on particle size can be found in Ref. (4), proving that the particle size can be an important factor affecting the solubility below 10 nm. An extreme conclusion can be obtained by substituting $\gamma = 50$ mJ/m^2, $M = 1000$ g/mol, and $\rho = 0.5$ g/cm^3 in Eq. (1). Even in this case, the solubility ratio between the 10-μm particle and that of an infinite size is below 1.01 times. The roughness of the surface and collisions between particles make such calculations less important. Therefore, the effect of particle size on the apparent solubility can totally be ignored in the IDM study.

Figure 1 shows examples of the time profiles of the concentration of the dissolved IDM. The concentrations reached constant values after 2 days in most cases. However, when the solid amount added, C_t, was very low at pH 5, a period of 5 days was required to attain the constant solubility value. The change in the surface morphology may have a critical role in this slow equilibration, because the constituent needs to be solubilized first to form the smooth surface. Therefore, the equilibration period for the following solubility measurements of IDM was set at 5 days. No degradation peaks were found in the HPLC chromatograms. The precipitates after 5 days were dried to be subjected to the X-ray diffraction study to confirm that the crystal form (γ-form) did not change during the equilibration.

Table III. Experimental Conditions for the Crystallization Study

pH	Initial C_t (mg/ml)	C_{DMSO} (mg/ml)	V_{DMSO} (μl/ml)	Final C_t (mg/ml)	C_i (mg/ml)	C_f (mg/ml)
5	0.2	20	5	0.3	0.12	0.011
	0.2	40	5	0.4	0.22	0.012
6	1	50	10	1.5	0.62	0.15
	1	100	10	2.0	1.12	0.16
	1	100	20	3.0	2.12	0.19
7	10	500	10	15	6.10	1.13
	10	1,000	10	20	11.1	1.16
	10	1,000	20	30	21.1	1.23

C_{DMSO}: Indomethacin concentration of the DMSO solution added, V_{DMSO}: volume of the DMSO added.

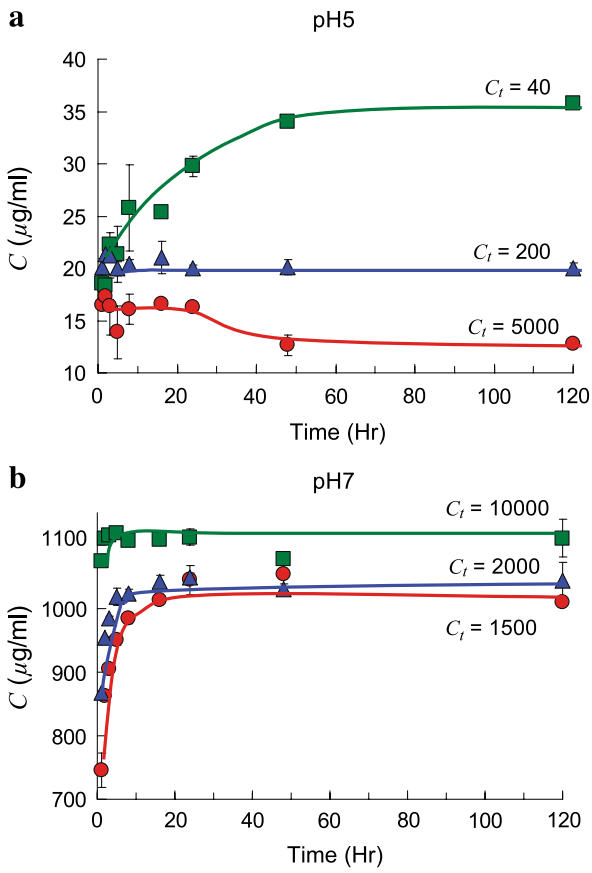

Fig. 1. Time dependence of indomethacin (IDM) solubility, C, at (a) pH 5 and (b) pH 7. C_t is the solid amount added (μg/ml). All measurements were done in triplicate. The standard deviations are shown as error bars, although most of the bars are hidden in the symbols.

The same procedure was applied to all the model drugs. Three days were long enough for the other drugs to reach the equilibrium state. The particle sizes of PHT, PDL, and TLB were 20–50, 30–40, and 30–50 μm, respectively, and did not increase or decrease during this period.

Impact of Solid Amount on Solubility

As indicated by Fig. 1, C_t affected the apparent solubility. Figure 2 shows the dependence of the solubility of IDM on the amount of excess solids, $C_{ex}(=C_t - C)$, after equilibration. Although the increase in the solid amount led to a decrease in the solubility at pH 5 and 6, an opposite tendency was observed at pH 6.5 and 7. The phase transformation of IDM can be expressed as

$$\mathrm{IDM_{Solid}} \underset{K_c}{\overset{K_d}{\rightleftarrows}} \mathrm{IDM_{Solute}} \tag{2}$$

where k_d and k_c are the rate constants of the dissolution and the crystallization, respectively. The time course of the solute concentration, C, can be written as

$$\frac{dC}{dt} = k_d S f_d(C) - k_c f_c(C, S) \tag{3}$$

where t and S are the time and surface area, respectively. $f_d(C)$ is a linear function of the difference between C and the equilibrium solubility, C_{eq}, when $C < C_{eq}$. It may simply be a constant when $C < C_{eq}$, because thermal perturbation is the only driving force of the dissolution. A general description for $f_c(C,S)$ is a difficult issue, because there are various expressions even for simply describing the rate constant of the crystal growth (16–19). The degree of supersaturation has generally been thought of as one of the dominant factors affecting this term. The apparent solubility seems to be determined by competition between k_d and k_c. In other words, if the dissolution rate is relatively faster than the crystallization rate (strictly speaking, the rate of the decrease in the solute concentration due to the crystallization), the apparent solubility should be larger than C_{eq}. Figure 2 shows that the apparent solubility became higher with an increase in the solid amount at pH 6.5 and 7, and vice versa at pH 5 and 6. Therefore, the dissolution and the crystallization rates seemed to be balanced at somewhere between pH 6 and 6.5.

Dissolution Rate of IDM Near Equilibrium Condition

The dissolution rate of IDM was evaluated by diluting the saturated dispersions prepared in advance. Assuming the initial concentration (after dilution) as C_i, we can approximate the evolution of the concentration by the following exponential decay function, ϕ_d.

$$\phi_d = \frac{C_f - C}{C_f - C_i} = \exp\left(-\frac{t}{\tau_d}\right) \tag{4}$$

where C_f and τ_d are the expected final solubility and the decay constant that describes the dissolution rate, respectively. C_f was obtained from the intercept of the $C_{ex} - C$ curves (Fig. 2). Averaged coefficients of determination in the fitting procedure were 0.82, 0.87, and 0.99 for datasets at pH 5, 6, and 7, respectively, indicating the validity of this analysis. Figure 3 shows the decay constants, τ_d, at each pH condition, as a function of the dilution rate. As can be seen, the faster dissolution rate (the lower τ_d) was observed for the higher dilution rate. This is reasonable, because the higher dilution rate means larger undersaturation, $C_{eq} - C$, which is the most important driving force for the dissolution process. A more important result is the dependency of the dissolution rate on the pH conditions. A faster dissolution rate was observed for the higher pH conditions over the entire dilution rate range examined. These dissolution rates reflect how fast the solute concentration reaches the equilibrium solubility.

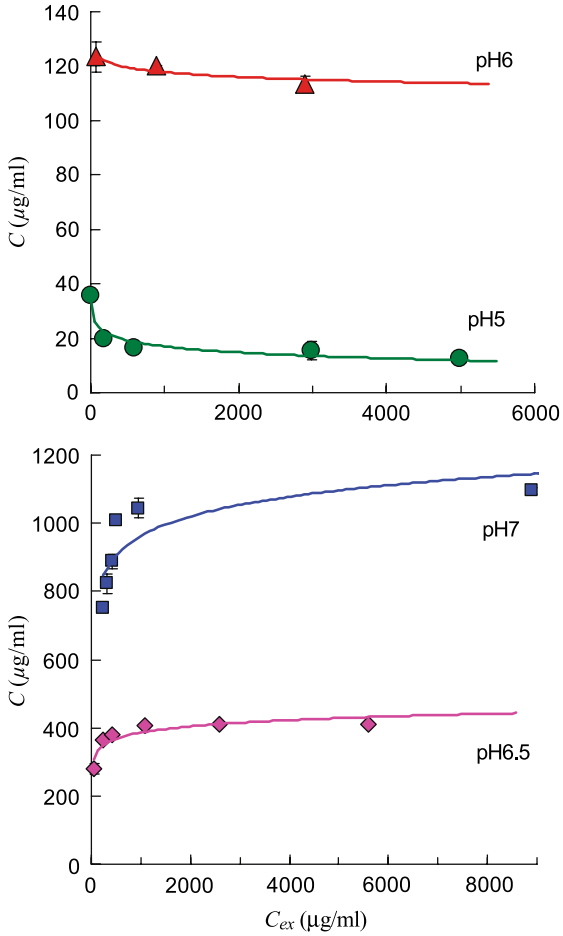

Fig. 2. Apparent IDM solubility as a function of the amount of excess solids, C_{ex}, at various pH as shown in the figure. All measurements were done in triplicate. The standard deviations are shown as the error bars, although most of the bars are hidden in the symbols. The best-fit curves for Eq. (6) are also shown.

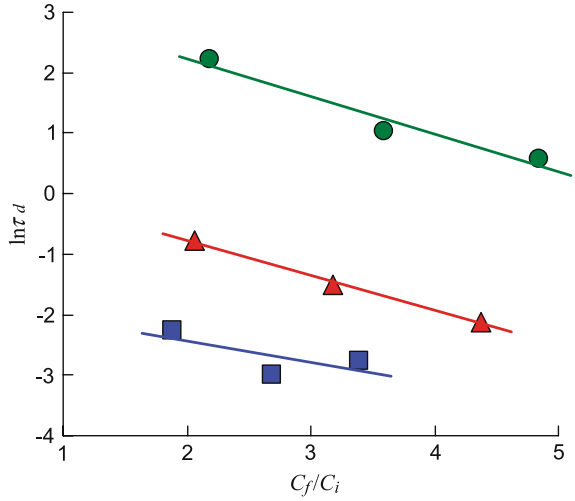

Fig. 3. Dissolution rate constant, τ_d, of IDM as a function of C_f/C_i at pH 5 (circles), pH 6 (triangles), and pH 7 (squares).

Crystallization Rate of IDM Near Equilibrium Condition

The crystallization rate of IDM was evaluated by observing the time dependence of the IDM concentration after injecting an IDM solution into saturated IDM dispersions. After introducing excess IDM into the saturated solution, a gradual decrease in IDM concentration was observed. This process can be described using the decay function, ϕ_c.

$$\phi_c = \frac{C - C_f}{C_i - C_f} = \exp\left(-\frac{t}{\tau_c}\right) \tag{5}$$

where τ_c is the decay constant that describes the change in the solute concentration due to the crystallization. C_i is the

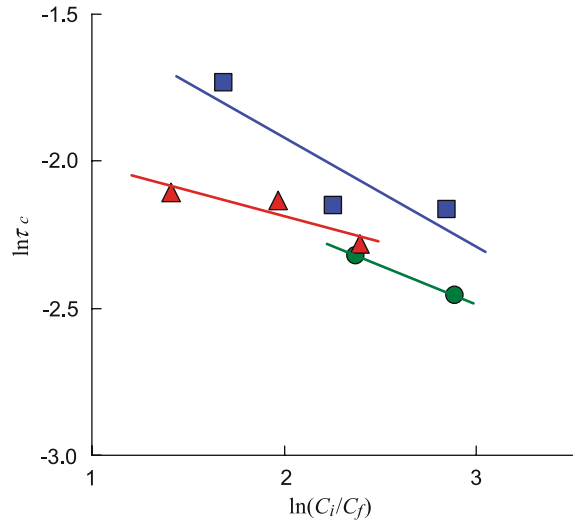

Fig. 4. Crystallization rate constant, τ_c, of IDM as a function of $\ln(C_i/C_f)$ at pH 5 (circles), pH 6 (triangles), and pH 7 (squares).

IDM concentration at the supersaturated state just after injecting DMSO solution in this case. C_f was obtained from the intercept of the C_{ex}–C curves as done for the dissolution process analysis. Averaged coefficients of determination in the fitting procedure were 1.00, 1.00, and 0.98 for datasets at pH 5, 6, and 7, respectively. Therefore, this exponential approximation was more effectively applied to the crystallization rate analysis than to the dissolution. Figure 4 shows the decay constants, τ_c, at each pH condition as a function of the supersaturation term, $\ln(C_i/C_f)$. As can be seen, the faster crystallization rate (lower τ_c) was observed for the higher supersaturation as has frequently been reported. As for the dependence on the pH condition, faster crystallization was observed for the lower pH over the entire supersaturation range investigated. However, the dependency of the crystallization rate on the pH condition was relatively small compared to the dissolution behavior.

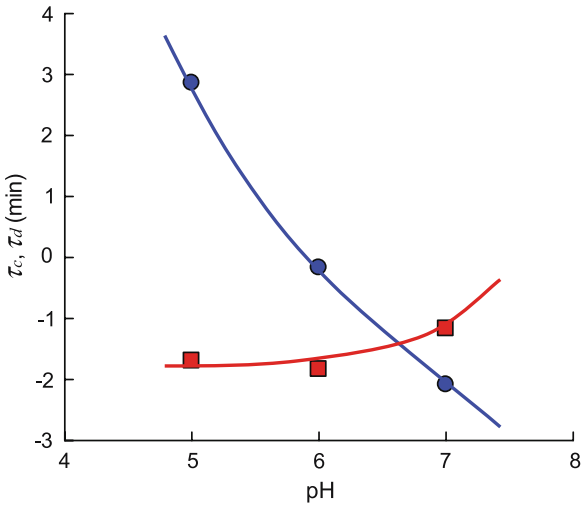

Fig. 5. τ_d (circles) and τ_c (squares) values at $C_f = C_i$ as a function of pH.

Comparison of Dissolution Rate and Crystallization Rate

The dissolution and crystallization rates of IDM at dynamic equilibrium can roughly be determined by extrapolating the linear fittings of Figs. 3 and 4 to $C_f/C_i = 1$ and are plotted in Fig. 5. Obviously, a much stronger dependency on pH conditions was observed for the dilution rate than for the crystallization rate. Although the charge on the molecules, which increases with the increase in pH in the case of IDM,

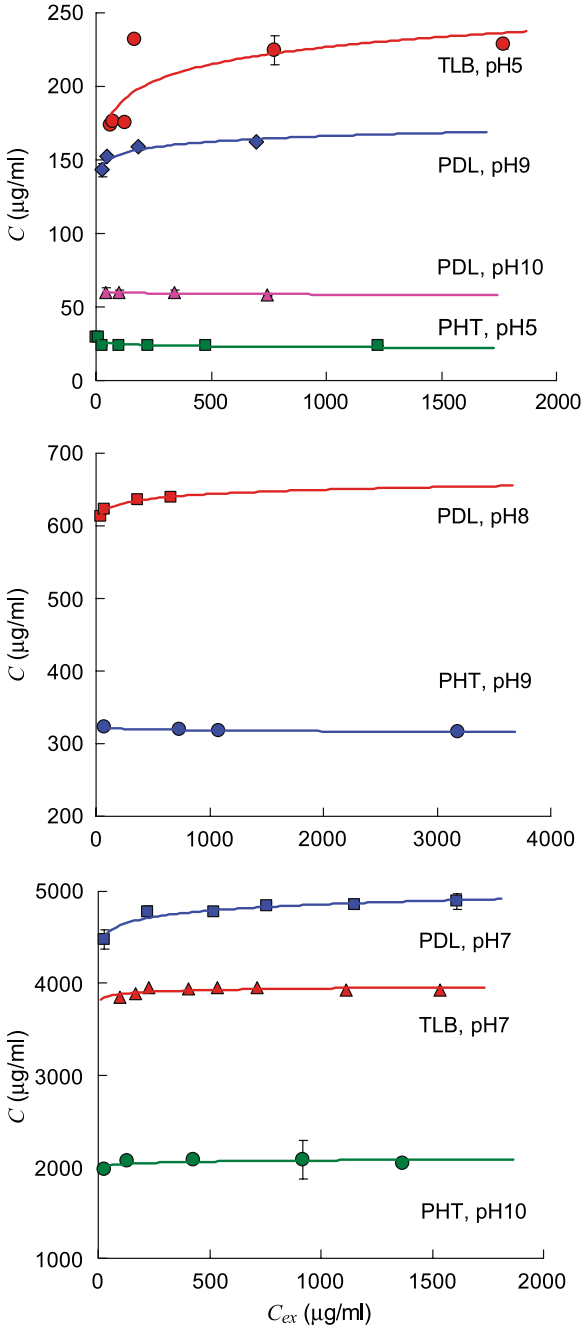

Fig. 6. Apparent solubility of the model drugs as a function of amount of excess solids, C_{ex}, at various pH as shown in the figure. All the measurements were done in triplicate. The standard deviations are shown as the error bars, although most of the bars are hidden in the symbols. The best-fit curves for Eq. (6) are also shown.

was expected to disturb the crystal growth dramatically, its impact on τ_c was not significant. A difference in the solubility itself seems to have much greater impact on the variation of the apparent solubility, because the dependence of τ_d on pH was very large. Comparison of τ_c and τ_d indicates that those values become equal at somewhere between pH 6 and 7. This supports the experimental observation, in which the excess solids increased the apparent solubility above pH 6.5 but decreased it below pH 6. In other words, the interpretation of this phenomenon in terms of a competition between the dissolution and crystallization rates is the most likely.

On the Role of Excess Solids: Generalization

Figure 6 shows the effect of the solid amount on the observed solubility of the other model drugs. As can clearly be seen, the excess solids affected the apparent solubility of all the drugs employed. PHT is an acidic drug with a pK_a value of 8.3 (20). Its apparent solubility slightly decreased with an increase in excess solids at pH 5, where it was hardly ionized. On the other hand, its apparent solubility increased with an increase in the excess solids at pH 10, where about 98% of the PHT molecules were negatively charged. TLB is also an acidic drug with a pK_a value of 5.3 (20). Its apparent solubility increased with an increase in excess solids at pH 5, where it was hardly ionized. Its apparent solubility was nearly constant at pH 7, where about 98% of the TLB molecules were negatively charged. PDL is a basic drug with a pK_a value of 8.8 (20). Its apparent solubility was nearly constant at pH 10, where only 6% of the PDL molecules were ionized. Its apparent solubility increased with an increase in the excess solids below pH 9.

The effect of the excess solids on the apparent solubility was quantified by the following equation.

$$C = a \ln (C_{ex}) + b \tag{6}$$

where a and b are constants; a is being used as a parameter to evaluate the effect of the excess solids on the apparent solubility. This function was selected simply because of its goodness of fit. As a representative solubility value, we tentatively employ C^*, where

$$C^* = a \ln (C^*) + b \tag{7}$$

Needless to say, the "true" equilibrium solubility value should be the best choice as the representative solubility value. However, this cannot be determined at this moment (as will be discussed later). Nevertheless, we need to obtain the representative value for normalizing the effect of the excess solids on the solubility values. The next option to select the representative solubility value is to fix the solubility/solid amount ratio. Therefore, C^* was employed (and it should work well for this purpose, because all that is required are "rough" solubility values).

Figure 7 shows a/C^* values as a function of C^* or percentage of the ionized molecules, which can be obtained by the following equation in the case of acids.

$$(\%\text{Ionized}) = 100 \times \left(1 - \frac{1}{1 + 10^{\text{pH}-\text{p}Ka}}\right) \tag{8}$$

In the case of bases, pH and pK_a need to be exchanged. Figure 7 clearly shows that the percentage of ionization has no correlation with the a/C^*, whereas C^* may be an important factor to determine a/C^*. Recalling that the dissolution rate of IDM had a much stronger dependency on pH than the crystallization rate, the relative importance of C^* may be explainable, because the ionization itself seems to have little impact on the effect of the excess solids according to the crystallization rate analysis. However, it should also be noted that the effect of the excess solids was by far the strongest for IDM. Therefore, there still remain some unknown factors affecting the apparent solubility.

Usually, when solubility is evaluated, little attention is paid to the amount of solids added. This is obvious from the fact that the amount of solid is rarely reported in literature. However, we have shown here that the amount of solid may significantly affect the observed solubility values. The most likely explanation for this is the competition between the

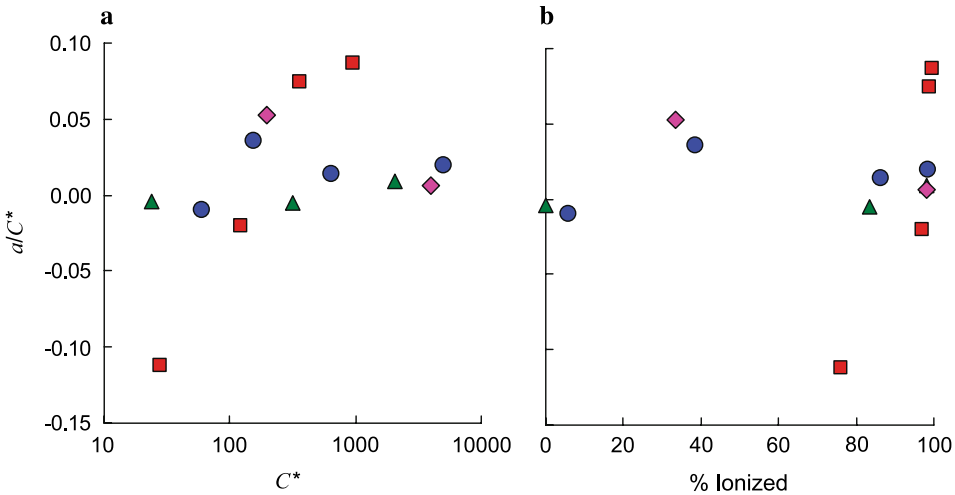

Fig. 7. a/C^* values as a function of (a) C^* or (b) percentage of the ionized molecules. IDM (squares), PDL (circles), PHT (triangles), and TLB (diamonds).

dissolution and crystallization rates. This should be one of the reasons for the variation in the reported solubility values shown in Table I. Therefore, we strongly recommend that the amount of solid introduced be reported in addition to the other conditions, such as time for equilibration, temperature, and reproducibility, when solubility measurements are conducted.

One important problem remains unsolved. How can we obtain the true solubility values? If our assumption is correct, it should be possible to obtain them by extrapolating the C–C_{ex} curve to $C_{ex} = 0$. However, it is obvious that Eq. (6) does not hold at the $C_{ex} = 0$ limit. On the other hand, the consistency of the apparent solubility values under a substantial amount of excess solids may suggest that those values were rather true ones. The effect of solid amount on apparent solubility values may not have critical impact on formulation studies as well as the screening process, because the change in solubility value was trivial in most cases from a practical viewpoint. Nevertheless, its theoretical interpretation is of great importance.

CONCLUSIONS

The effect of the amount of excess solids on apparent solubility was investigated. When IDM was used as a model drug, apparent solubility decreased with an increase in solid amount at pH 5 and 6. On the other hand, it increased with an increase in solid amount at pH 6.5 and 7. The crystallization and dissolution rates of IDM decreased and increased, respectively, with an increase in pH, and became equal at between pH 6 and 7. Therefore, apparent solubility was most likely affected by the balance between crystallization and dissolution rates. The apparent solubility of other model drugs showed the same trend, although its dependency on solid amount was not as significant as in the case of IDM. The effect of solid amount should be one of the reasons for the difference in the reported solubility values, and thus the amount used in experiments should be reported in papers.

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