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Rapid Communication

The relationship between particle size and solubility

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It has been observed experimentally that the reduction in particle size of a sparingly soluble material results in an increased rate of solution. This observation is in line with the Noyes Whitney equation, which is regularly used to describe the process of dissolution of solid drugs:

$$\frac{dm}{dt} = \frac{DA(C_s - C)}{h} \quad (1)$$

[where the rate of change of mass dissolved (m) with time (t) is related to the diffusion coefficient (D) through a static layer of liquid of thickness h, and C_s is the equilibrium solubility and the amount dissolved at time t (C)] * in that an increase in the surface area of a drug will result in a more rapid dissolution process, particularly under sink conditions (where $C \ll C_s$). This kinetic observation is clear and unambiguous, however, experimental results also lead to the conclusion that the value of C_s can be influenced by a change in particle size. For example, Banker and Rhodes (1979) review studies which have shown that the micronised form of griseofulvin reaches an apparent C_s of approx. 3 mg/100 ml, whilst the 'crystalline' form of the drug reaches C_s of less than 2 mg/100 ml. In this example the drug was kept in equilibrium with the solvent (water) for 20 h. Sjokvist and Nystrom (1988) have reported that the solubility of griseofulvin varies between 7.9 and 11.9 mg dm^{-3} depending upon the method used to produce a solid dispersion of the drug in polyethylene glycol 3000.

Equilibrium thermodynamics defines equilibrium as being the point when the Gibbs free energy term (ΔG) is equal to zero and, for two phases (α, β) in equilibrium that $a_i^\alpha = a_i^\beta$ (i.e., the activities are equal). These definitions do not, and cannot, incorporate any statement about the time required to achieve thermodynamic equilibrium. For example, for:

$$H_2(g) + 1/2O_2(g) \rightarrow H_2O(v)$$

$\Delta G^\ominus = -228.4$ kJ mol^{-1} (Atkins, 1990). This large negative ΔG means that the reaction is, on thermodynamic grounds, spontaneous; however, this reaction will not proceed in the absence of catalyst. Thus, practically, hydrogen and oxygen gas can co-exist for very long periods of time. As, by definition, a catalyst changes the rate at which equilibrium is achieved, but does not alter the position of equilibrium itself, the system in which these two gases are mixed in the absence of a catalyst may appear to be at equilibrium, but is

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* It is interesting to note that the Noyes Whitney equation is often misquoted, by substituting dc/dt (i.e., a rate of change of concentration with time) for dm/dt. Such an error results in an equation for which the units do not balance.

clearly not at its true thermodynamic equilibrium.

When equilibrium solubility is the subject of investigation, it is usual to specify a finite time for the experiment (this may be determined by factors such as the sensitivity of the technique adopted to determine the solubility, and the stability of the drug in solution). Here it appears, a practical definition of equilibrium is adopted and not the time independent thermodynamic equilibrium. The necessary condition for a rapid (i.e., within the usual time scale of a practical solubility determination) achievement of thermodynamic equilibrium is that a reaction mechanism of low Gibbs energy of activation be available. This is provided for by the inclusion of a catalyst in the hydrogen/oxygen example.

The case for the increase in solubility with reduction in particle size

The Gibbs-Kelvin relation — The fundamental basis for the observation that size may influence solubility is found in the Kelvin equation, which gives the increase in pressure for a curved surface, by comparing the pressure in a small bubble (of radius r) P_r with that in an infinitely large one (P_∞):

$$\log\frac{P_r}{P_\infty} = \frac{2\gamma V}{rRT} \qquad (2)$$

where γ is the interfacial energy, V represents the molar volume, R is the gas constant and T denotes the absolute temperature.

It is argued that the Kelvin equation is equally applicable to the solid-liquid interface, and that activity can be substituted into Eqn 1 in place of the pressure terms. Replacing the activity terms with solubilities (which will be designated by S), as activity coefficients are effectively set equal to unity in the dilute solutions considered here, produces the so-called Gibss-Kelvin relation.

The Gibbs-Kelvin relation is used as a model for crystallisation (e.g., Parfitt, 1973), whereby homogeneous nucleation will occur when a stable nucleus is formed; a stable nucleus being one which has exceeded a certain size and thus is described as having a lower solubility (and consequent longer existence). It is also considered as a method by which solid-liquid interfacial energies can be determined from changes in solubility as a function of size (Adamson, 1976).

Many pharmaceutical texts report variations of the Gibbs-Kelvin relation, for example, in the textbook on Physical Pharmacy by Martin et al. (1983), this equation is described as being valid for small particles in the micrometre range, and is presented in the form:

$$\log\frac{S_r}{S_\infty} = \frac{2\gamma V}{2.303RTr} \qquad (3)$$

In Bentley's Textbook of Pharmaceutics (1977), the equation is given in the following form:

$$\ln\frac{S_r}{S_\infty} = \frac{2\gamma M}{\rho rRT} \qquad (4)$$

In this equation, the molar volume is replaced with a molecular weight (M) and a density (ρ) term, which results in a balance in terms of dimensions. The exponential form of Eqn 3 is given by Banker and Rhodes (1979) where it is stated that, for very small particles, the saturation solubility of a drug may increase as particle size decreases. It is reported (Rawlins, 1977) that this equation is valid only for sparingly soluble particles of less than 1 μm in size.

A very similar version of this equation was presented by Richards (1988) in which it is stated that the "changes in interfacial free energy that accompany the dissolution of particles of varying sizes cause the solubility of a substance to increase with decreasing particle size". This could be interpreted to imply that the change in interfacial energy is due to the presence of the dissolved solute, which is clearly not the basis of the equation.

The description of the effect of particle size and solubility given by Florence and Attwood (1981) (although discussion of this is absent from the more recent edition), at least in part, raises the issue of equilibrium states and of kinetics: "The rate of solution is primarily a function of surface area. Reduction of particle size increases the surface area and the rate of solution increases. Reduction of particle size in the micro-

scopic range (to c 1 um) does not affect solubility". Florence and Attwood (1981) to on to note that particles of a very small size may have a changed equilibrium solubility due to the high surface to volume ratio, and small number of molecules in the bulk.

The case against particle size affecting solubility
Thermodynamic considerations — Considering Henry's Law for the case of infinite dilution, it is possible to demonstrate that the chemical activity of a pure solid is unity. This is a central and certain aspect of thermodynamics, i.e., that the standard state for a given solid is unity. If a solid has an activity of 1, it follows that although changes in its particle size may affect that rate of solution (i.e., a change in surface area in Eqn 1), such size changes cannot affect the equilibrium solubility. Effectively, a change in particle size can be regarded as analogous to a catalyst, i.e., it can alter the rate at which equilibrium is achieved, but cannot alter the (time independent) equilibrium value.

It must be asserted, on the basis of thermodynamics, that apparent changes in equilibrium solubility reflect changes in the rate at which equilibrium is achieved (*NB*: workers ascribe an arbitrary end point to processes for experimental convenience, this may not reflect the true equilibrium), and possibly the absence of a route by which equilibrium can be achieved. Such arguments are followed in other texts, for example, Hiemenz (1986) shows that a rate law can be developed which relates particle size growth to collision frequency, etc. and further demonstrates that systems consisting of small particles are in some unstable, or metastable, state.

Supersaturation — Kinetic factors are responsible for many apparent differences in equilibrium solubility, however, the case of very small particles must be given special attention. Most of the workers who quote the Gibbs-Kelvin relation state that its applicability is in the sub-micron range.

Relating to the use of the Gibbs-Kelvin relation in nucleation studies, it is argued that supersaturated solutions are thermodynamically unstable, and can be expected to crystallise by a swarm of molecules coming together. However, these extremely small particles have an increased interfacial energy with respect to the solvent and are thus more rapidly soluble, and instead of growing they will dissolve. Crystallisation will only occur when a sufficiently large particle is formed, which will remain in existence long enough to allow further growth. This is also a kinetic phenomenon, where the properties of the small sized particles prevent progress to the true equilibrium state (i.e., the formation of large particles) from occurring. In the case of solubility, the extremely small particles are forcing a thermodynamically unstable supersaturation. This may appear to be an equilibrium, within the time scale of the experiment, but does not represent a true equilibrium state. The true equilibrium for the solid phase, and for which $a_{solid} = 1$, is that of the large particle (greater than 1 μm); thus small particles should eventually transform to large particles in time unlimited experiments (given the appropriate mechanism of low activation energy).

A further analogy is that of supercooling, taking water as an example; it is commonly acknowledged that water will freeze at 0°C, however, water without any particulate contamination does not freeze until approx. −40°C (e.g., Alberty, 1987); this example of supercooling demonstrates again that the true phase equilibrium cannot be established unless there is a suitable route available (i.e., particulate matter to act as nucleation centres). Returning to the question of solubility, in all cases the equilibrium state must be the existence of the larger particles, which exhibit the only true equilibrium solubility; any other apparent solubilities exist as metastable equilibria.

Polymorphism is another curious situation as it is practically observed that different polymorphs have different solubilities (notionally different equilibrium solubilities). On the basis of the arguments raised above this cannot be true. In reality, the true thermodynamic equilibrium is between the stable form of the solid and the dissolved solute, other apparent equilibria refer to different (thermodynamically unstable, i.e., not at equilibrium) states. It is, therefore, not surprising that certain polymorphs dissolve to produce concentrations higher than C_s, and then rapidly reprecipitate until the true equilibrium solubility is reached. Other pseudo-equilibria may exist (for

different polymorphs and small particles), but only because the conditions that prevail do not allow the equilibrium to be reached.

Whilst it is logical to utilise the elevated solubilities that can be achieved by polymorphs and small sizes for pharmaceutical gain, it is incorrect and inappropriate to describe these apparent equilibria as being the true thermodynamic equilibria.

In conclusion, whilst changes in particle size may apparently change equilibrium solubility, thermodynamically this is unacceptable, and must reflect a failure to reach a true equilibrium. This in no way negates the fact that apparent differences in equlibrium solubilities exist for different forms of the same solid. It is wise to utilise all available means for pharmaceutical advantage, and enhancement of the solubility of sparingly soluble materials is often a considerable challenge, but it remains important that the fundamental theory that relates to these practical observations is not obscured.

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