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On the solubility advantage of a pharmaceutical's glassy state over the crystal state, and of its crystal polymorphs

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ABSTRACT

At equilibrium, the saturation solubility and vapor pressure of a material in a state of high free energy are greater than in its state of low free energy. This knowledge from classical thermodynamics is currently used for increasing the solubility of crystalline pharmaceuticals by producing them in their glassy state, or in other solid states of high free energy. The ratio of the apparent saturation solubility of these solids to that of a crystal, calculated from the thermodynamic data of the pure solute, ϕ_{cal}, is called the solubility advantage, and it is used as a guide for increasing the solubility of a pharmaceutical. We argue that the ϕ_{cal} differs from the measured solubility ratio, ϕ_{meas}, because, (i) ϕ_{cal} is independent of the solvent, but ϕ_{meas} is not so, (ii) ϕ_{cal} would increase with the dissolution time monotonically to a constant value, but ϕ_{meas} would first reach a maximum and then decrease, and (iii) approximations are made in estimating ϕ_{cal} and the effect of thermal history on high free energy solids is ignored. On the other hand, ϕ_{meas} is affected by, (a) another chemical equilibrium in the solution, *e.g.*, hydrogen-bond formation and ionic dissociation, (b) the production method and thermal history of a glass or an amorphous samples, and (c) mutarotation in the solution, isomerization or tautomeric conversion in the solid. We also discuss the effects of structural relaxation and crystallization on ϕ_{meas}. The ϕ_{meas} value of a (crystal) polymorph would be affected by all the three, and further if the polymorph is orientationally disordered. We provide evidence for these effects from analysis of the known data. The ϕ_{meas} value is preferable over ϕ_{cal}.

1. Introduction

A structurally disordered solid has a higher free energy than its crystalline solid. Therefore, according to the classical thermodynamics, the saturation solubility, vapor pressure, and chemical reactivity of a structurally disordered solid are expected to be higher than those of its crystal. This knowledge has been put to use in designing curative drugs (pharmaceuticals) by conversion to a structurally disordered solid which, at least initially, dissolves more, and more quickly, than its crystalline solid, *i.e.*, to enhance their bioavailability. The free energy difference between a disordered solid and its crystal form is calculated from the thermodynamic data, and then used to estimate the ratio of the solubility of a disordered solid to that of its crystal state. In an extensive discussion of thermodynamics of amorphous solids and glasses, Grantscharova and Gutzow [1] reviewed the expressions for the solubility, vapor pressure, and chemical reactivity of these materials, analyzed the available data on the solubility of amorphous and crystalline states of Se in CS_2, of As_2O_3 in water and of SiO_2 in (normal and supercritical) water, and reported their measurements of the temperature dependence of the solubility of the glassy and crystalline states of phenolphthalein in water [1]. We also note that a crystal surface has a higher free energy than its bulk, and therefore finely powdered crystals also are more soluble, have a higher vapor pressure, and higher chemical reactivity than large crystals of the same material.

Thermodynamic expressions for solubility, vapor pressure, and chemical affinity in terms of the enthalpy and entropy of a supercooled melt were used by Gutzow in 1970 [2]. In Section 3.12 of a comprehensive monograph on the vitreous state, Gutzow and Schmelzer [3] reviewed the thermodynamic relations between the free energy and solubility, vapor pressure, and chemical affinity of the vitreous state. They fully adapted the available formalism in the literature from 1908 to 1970 [4–9], which they noted. The formalism had been used in discussing the properties of (metastable) supercooled liquids and of (non-equilibrium) glassy states by Simon [5,9], but they [1,3] provided a comprehensive account as well as the data on the solubility of the glassy and crystalline states of phenolphthalein, a pharmaceutical and an alkalinity indicator, in water at different *T*, and at different times

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during its dissolution at a fixed T. They also quantitatively described the kinetics of precipitation of the solid from its supersaturated solution by using the equations for molecular diffusion, and re-examined the problem of crystal growth at a fixed T with glassy solids used as a constant source of super saturation, and finally discussed the possibility of crystallization of a glass *via* a third phase at T below the glass-liquid transition temperature, T_g. Simon [5,9] and others [1–4,6–8] had outlined the difficulties in accepting the definition of solubility of glasses, and had indicated that for comparison with thermodynamic expressions, the only way to perform a reliable measurement of the solubility is to consider practically zero stay-time of the glass surface in contact with the solution. Thus, the effect of any changes at the interface of the solid-solute and its solution, with time, can be excluded. In such a case, thermodynamic expressions would give the instant saturation solubility of a solid in contact with an infinitesimal amount of the solvent. Gutzow and Todorova [10] have extended the discussion on this subject, describing glasses as systems of increased solubility and high chemical reactivity, and as sources of accumulated energy.

In the plot of the concentration of phenolphthalein solute in the glassy state (T_g = 353 K, [1]) against the dissolution time in water at 295 K in Fig. 11 [1], Grantscharova and Gutzow showed that the concentration does not stay strictly constant after reaching the broad plateau, but tends to slightly decrease after ~300 min. From these plots, we estimate that the ratio of the glass to crystal state solubility after ~300 min is ~7 at 295 K and ~9 at 286 K. They provided its solubility-temperature diagram, namely the plots of the solubility values for glass at 14 temperatures, and for crystal at 15 temperatures (Fig. 16, [1]), showing that the solubility of its crystal solute decreases more rapidly on cooling than that of the glassy solute, *i.e.*, the solubility ratio, ϕ_{meas}, increases with decrease in T, and they provided the solubility data also at T of 334 K (Fig. 12, [1]), 281 and 332 K (Fig. 14, [1]). Moreover, they performed experiments on the growth of phenolphthalein crystals at the expense of dissolution of its glass in the same saturated solution (Fig. 5, [1]), discussed the dissolution kinetics in terms of the rate of dissolution of both crystalline and glassy states by using the Nernst equation with and without precipitation of the solute from the solution (Fig. 4, [1]) and demonstrated that the glass samples themselves serve as active substrates in the crystallization process of supersaturated solutions. Their paper [1] and Section 3.12, [3] may be consulted for a comparison between the experimental data and thermodynamic predictions and for further analyses.

One admits that there are limitations for using thermodynamic expressions for determining the vapor pressure, solubility, and chemical affinity, and it was carefully stated [3]: "The main postulate, underlying the thermodynamic definition of vapor pressure, solubility and chemical affinity of a glass, applied here, is the following: These quantities are determined by the respective values of the thermodynamic functions of the metastable under-cooled melt at the freezing-in temperature." They also noted that [3]: "If variations of the glass-vapor or glass-solution interface determine to a large extent the vapor pressure or the solubility, then there is indeed no point in assuming well-defined values of vapor pressure or solubility of a glass." We agree with these statements. However, it was also concluded [3]: "The agreement of experimental results and theoretical predictions for these properties gives an additional proof of the expressions for the thermodynamic potentials, derived in Sects. 3.3 and 3.5." On the basis that the theoretically predicted solubility ratio, ϕ_{cal}, is expected to be independent of the solvent, and the experimental solubility ratio, ϕ_{meas}, depends upon the solvent, it seems that this proof [3] may not be generally valid. Thermodynamic expressions for the effects of the cooling rate, structural relaxation, etc., provided in [3], although relevant, are too detailed to be included here. Readers may consult the original papers in [1,3].

It should be stressed that the results obtained by using the equilibrium thermodynamics equations for a non-equilibrium condition can only be approximate. This is especially so when we recognize that a steady state concentration is observed when the rate of dissolution of a solute amorph becomes equal to the rate of precipitation of the solute from the solution in a different form as a deposit on the existing solute particle surface [1,3], and that too occurs only transiently. Because of that, it seems almost impossible to achieve an equilibrium state between a solute in solution and its amorph particle or the particles surface macroscopically dispersed in the bulk of a solution. Nevertheless, we acknowledge that despite their strong relevance, the studies reported in [1,3] were overlooked by the pharmaceutical research community. On the other hand, the solubility studies of pharmaceuticals, reported since 1963, were already based upon, or interpreted in terms of, the relation between the free energy and solubility as used in [1–3]. Perhaps, a comparative discussion of the solubility ratio data reported since 1963 and the conclusions on the solubility ratio [1,3] would be helpful in future investigations.

A glass is formed by melting a crystalline solid and supercooling the melt. Other methods are also used for producing structurally disordered solids of high free energy. Briefly, these methods are: deposition of vapor on a cold substrates, ball-milling a crystal, collapsing a crystal under a high pressure, shear-amorphizing a polycrystalline solid, electrochemical deposition from a solution, gas phase chemical reactions, oxidation, bombardment of crystal by high energy particles, subjecting crystal to a shock wave [11], and lyophilization, *i.e.*, freezing the material and then reducing the surrounding pressure to allow the frozen water in the material to sublimate directly from the solid phase to the gas phase.[1] These solids show an unusually high loss of enthalpy and volume before reaching the equilibrium state on heating and have properties that qualitatively differ from those of glasses. To distinguish them from glasses, such disordered solids are called amorphous solids. This distinction, however, is not maintained in the pharmaceutical literature, where glasses and all disordered solids produced by different methods have been called amorphous solids [12–16]. For convenience here, we refer to all these high free energy solids as "amorph",[2] and use the term glass where distinction is required. We exclude from our discussion, fine powders, and nano-crystals whose surface energy per unit mass is exceptionally high.

It has been known for more than a century that crystal polymorphs differ in both their enthalpy and entropy and therefore in their free energy. This difference is expected to cause a difference between the saturation solubility, vapor pressure, and chemical reactivity among the polymorphs: a crystal polymorph of higher free energy would have a higher solubility, vapor pressure, and chemical reactivity than a crystal polymorph of lower free energy. Historically speaking, among the earliest studies on the

[1] Lyophilization is a technique widely used in pharmaceutical industry to recover a solid from a solution. Attempts are currently made to produce pharmaceuticals not only in the glassy state but also in the amorphous state by using ball-milling, or lyophilization, which produce solids of free energy much higher than that of a glass, and then attempts are made to stabilize their amorphous state against crystallization. (The often-found variability in saturation solubility of pharmaceuticals produced by lyophilization was attributed to unintended production of amorphous particles during the process, and of their crystallization with time. It is estimated that more than half of biological pharmaceuticals are stored in the form of freeze-dried, or lyophilized, powders. Although freeze-drying prevents protein aggregation and degradation processes that can occur in aqueous solution, many biologicals exhibit reduced therapeutic efficacy when they are rehydrated from the powdered state.)

[2] For convenience, we henceforth refer to the thus produced fully non-equilibrium amorphous solids as amorphs. Even though their properties differ from those of glasses, and they show a large enthalpy decrease on heating, we discuss their solubility and solution properties together with those of the glassy state of pharmaceuticals.