



Electric field for increasing the solubility of glass - a much sought after pharmaceutical advantage

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ABSTRACT

A glass is usually formed by supercooling a liquid under ambient conditions. It can also be formed by supercooling under the influence of a static electric field, E , and used, after removing E , in the electrically polarized state as glass-electret. On the basis of the relation between E and the free energy, we formally deduce that solubility, dissolution rate and vapor pressure of a glass-electret would be higher than the corresponding values of normally formed glass. Calculations performed by using generic values show that increase in solubility would be by about 5–19%, and is likely to be more for a pharmaceutical glass. Further, we propose that solubility advantage of a pharmaceutical may be more accurately determined by measuring the vapor pressure. Electrets formed from liquid crystal and orientationally-disordered crystal state of pharmaceuticals would show similar increase in solubility and vapor pressure. The conclusions are important because of the need to increase the bioavailability of orally-, or intravenously-administered poorly soluble compounds whose molecules enable a therapeutic change in human physiology.

1. Introduction

Effect of an external electric field, E , on static dielectric permittivity, ϵ_s , of liquids has been of interest since Herweg's findings [1] in 1920, that an electric field used to measure ϵ_s changes the value of ϵ_s [1–4]. Exact relations between ϵ_s and E for *non-interacting* dipolar molecules have been known since the Debye's theory [2] of dielectric saturation. The effects of E on the structure of a liquid and on its molecular isomerization were originally found by Piekara and Piekara in 1936 [3,4]. Since these findings, the thermodynamic aspects of dielectrics [5–7] have been variously studied and reviewed [8–25].

An electric field induced change in the thermodynamic properties of a liquid has experimentally observable consequences for its molecular dynamics. Previously, we used the Fröhlich equation [7] for the effect of electric field on the entropy to show that the relaxation time and viscosity of a liquid would increase under the influence of an electric field. Hence the temperature of its liquid to glass transition, $T_{l \rightarrow g}$, would slightly increase [24,25]. Interest in the subject of the effect of E on the properties of a liquid has grown enough that recent studies have been reviewed in two articles in the year 2017 [26–28]. Approach to this subject in these articles, however, differ: Lunkenhimer et al. [26] discussed the main mechanism that can give rise to non-linear dielectric response, and Richert [27] provided “a guided tour” of non-linear dielectric effects in liquids. In 2017, Gadige et al. [28] provided an insightful discussion of the non-linear dielectric effects in the context of

current theories of glass formation. Here we describe a further consequence of an electric field, namely its effect on the saturation solubility of a glass. We use the premise that application of a static electric field increases the free energy of a liquid, and thereby formally show that increase in the static electric field under which a glass is formed by supercooling a liquid would increase the solubility, σ , the vapor pressure, p^{vap} , and the dissolution rate, Γ , of the glass.

Relations between the free energy, σ , p^{vap} , and Γ of a solid have been known from the works of several groups since the 1930s, and the concept underlying these relations have been critically examined [29–41]. In 1934, Parks et al. [29] also tested the relation between the free energy and σ by experiments. They measured the solubility of the glassy state and of the α -crystalline state of glucose in methanol, in ethanol, and in 1-propanol as solvents and found that the solubility of the glassy state of glucose is 16–24 times the solubility of its α -crystalline state. Moreover, the ratio of the solubility of glass to crystal depended upon the nature of the solvent, the highest ratio was for methanol as solvent.

When a dipolar liquid is supercooled under the influence of a static electric field, E , and it does not crystallize, it becomes an electrically polarized glass. After removal of the electric field at a low temperature, it becomes a glass-electret - a name akin to magnet. By using generic values of ϵ_s and of the molar volume, we provide an illustrative calculation of the increase in solubility of a glass-electret over a normally formed glass. The increase is expected to be greater for compounds of

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high molar volume, and of those compounds whose molecules have a tendency to form zwitter-ion dipoles, or to form ion-pair dipoles of high dipole moments. We also briefly discuss the properties of a glass-electret, its difference from a glass and its solubility optimization. The effect of an electric field on the free energy is substantial even though its effect on the entropy is small [24,25]. We also propose that measurements of vapor pressure would provide a simpler and more accurate method of determining the decrease in the free energy, σ and Γ during structural relaxation of a glass-electret, and during its crystallization.

A significant part of the pharmaceutical industry's research is devoted to finding methods for increasing the aqueous solubility of those compounds whose molecules enable therapeutic change in human physiology. The majority of these compounds are poorly soluble in water [42]. Nevertheless, they have shown the potential for use in treatment of cancer, cardiovascular, HIV, and other maladies. (See Refs. [42–45] for details.) Therefore, such compounds have to be dissolved in harmful solvents for the purpose of clinical trials, and for drug formulation. The industry recognizes that any increase, howsoever small, in σ and Γ of an orally, intravenously, and topically administered drug would be significant because increased solubility would reduce the amount of harmful solvent. Several of the commercially available solid drugs are now formulated by using their glassy state in order to increase their bioavailability by increasing their σ and Γ .

In contrast, research in academic institutions has become focused on the *molten state* of commercially available crystalline pharmaceuticals, especially on the dielectric relaxation features and crystallization kinetics of their supercooled liquid state. In the numerous papers published since 2006, such studies have served to support the already known features of molecular dynamics and crystallization of molecular and polymeric liquids during supercooling and aging. Unfortunately, these studies have introduced in the pharmaceuticals literature the debated methods of data analyses and conclusions, and unsettled terms used for describing the features of supercooled liquids. It is not obvious how such studies are related to the solubility of a drug, or else how they help in understanding its curative attributes.

The study reported here is on *glass*. Its sole intention is to provide a theoretical basis for increasing the solubility of a curative compound by producing its electrically polarized state. Therefore, this study is distinguished from previous studies of the relaxation of a pharmaceutical's melt. We hope that the thermodynamics-based formalism of the effect of an electric field provided here and the subsequent discussion would be helpful in the pharmaceutical industry's attempts to develop poorly soluble compounds as viable drugs.

2. Electric field and free energy

By using the static electric field, E , as a variable, Guggenheim [5], Koenig [6], Fröhlich [7], and Landau and Lifshitz [13] provided formulae analogous to the Maxwell's relations in thermodynamics. Thus they related the dielectric properties of a material to thermodynamic effects. Briefly, these formulae are used to describe the effects of E on internal energy, volume, enthalpy, and entropy of a material by using the static permittivity, ϵ_s , as the sum of contributions from electronic, vibrational and (dipole) orientation polarizations. Here we consider the effect of E only on the free energy, G .

Application of a static electric field increases the free energy, G . According to Fröhlich [7],

$$G(E) = G(0) + V_m \left(\frac{\epsilon_0}{2} \right) \epsilon_s E^2; \Delta_E G = V_m \left(\frac{\epsilon_0}{2} \right) \epsilon_s E^2 \quad (\text{in J mol}^{-1}), \quad (1)$$

where $G(E)$ is the free energy under the influence of E and $G(0)$ that without its influence, V_m is the molar volume at the measurement temperature, $\epsilon_0 (= 8.854 \times 10^{-14} \text{ F cm}^{-1})$ is the permittivity of free space, and $\Delta_E G$ is the E -induced change in G . (The term $1/4\pi$ in the original description [7] is equal to ϵ_0 in the SI units and $1 \text{ J} = 1 \text{ FV}^2$. We use E in Volts cm^{-1} .) By substituting for ϵ_0 in Eq. (1),

$$\Delta_E G = 4.427 \times 10^{-14} V_m \epsilon_s E^2 \quad (2)$$

A decrease in T increases ϵ_s of most liquids and solids, but it decreases ϵ_s of some liquids [46]. Here we consider the glassy state of only those liquids whose ϵ_s increases with decrease in T . Their $\Delta_E G$ for a fixed E would increase with decrease in T .

When a liquid under the influence of E is cooled, polarization fluctuations, which may not be the same as the density and structure fluctuations, become progressively more slow until they kinetically freeze on an experiment's time scale. Hence, a supercooled liquid becomes a glass under the influence of E . This glass is in an electrically polarized state, *i.e.*, a certain magnitude of electrical polarization is kinetically-frozen in its structure, and its properties would be distinguished from those of a glass formed by supercooling a liquid without the application of E . It was suggested that a liquid of high ($d\epsilon_s/dT$) would become a polarized glass when E is increased isothermally [24,25], and, the glass would become a liquid again when E on the glass is thereafter decreased isothermally. Preliminary experiments mentioned in Ref. [24] had shown that viscosity of a liquid increased under the influence of E .

The protocol for forming a glass-electret is illustrated in the top panel of Fig. 1. An electric field is applied to the liquid at point a , and its magnitude increased to polarize it significantly (point b). The liquid under the influence of fixed E is supercooled from b to d . During the supercooling, it vitrifies and becomes polarized glass at c , where $T = T_{l \rightarrow g}^E$, a value slightly higher than $T_{l \rightarrow g}^{E=0}$ [24,25]. The glass is then cooled from c to d , the static field E is removed and the state of the glass reaches point e . The state of glass at point e is a glass-electret, with stored-in electrical charge.

As mentioned earlier here, decrease in T increases ϵ_s of most liquids. The increase occurs according to the Curie-Weiss equation, $\epsilon_s - \epsilon_\infty = (T - T_c)^{-1}$, where T_c is the extrapolated temperature at which $\epsilon_s \rightarrow \infty$. The limiting high-frequency permittivity of orientation polarization, ϵ_∞ , is equal to the sum, ($n^2 + \Delta\epsilon_{ir}$), where n is the optical refractive index and $\Delta\epsilon_{ir}$ is the contribution to permittivity from vibrational polarization whose consequences are observed in the far-infrared region of the spectra. The quantity $d\epsilon_\infty/dT$ is insignificant in comparison with $d\epsilon_s/dT$ and, therefore, $[d(\epsilon_s - \epsilon_\infty)/dT] \cong d\epsilon_s/dT$. As the ϵ_s value increases with decrease in T , electrical polarization for a given E increases, more rapidly at low T than at high T , as long as dipolar fluctuations occur. When $T_{l \rightarrow g}^E$ is reached on continuous supercooling, the time scale of dipolar fluctuations would become equal to an experiment's time scale, and further supercooling would produce a polarized glass or *glass-electret* at $T < T_{l \rightarrow g}^E$. On further decrease in T , its polarization would remain (approximately) constant. This is illustrated in Fig. 1 (middle panel) where the equilibrium polarization for a fixed E is plotted against T . It increases progressively more rapidly with decrease in T , as the temperature T_c of the Curie-Weiss equation is approached.

When a liquid under the influence of E is supercooled at a certain rate, q_c , the polarization magnitude would kinetically freeze at $T = T_{l \rightarrow g}^E$ for that q_c . (We do not assign the values of the α -relaxation time, τ_α , or of the viscosity, η , at $T = T_{l \rightarrow g}^E$ for a given q_c , because their values at $T = T_{l \rightarrow g}^E$ generally depend upon the criteria used for glass formation, and are shown to be inconsistent with experimental data [47].) When q_c is high, $T_{l \rightarrow g}^E$ is high and the frozen-in electric polarization of a glass is low; when q_c is low, $T_{l \rightarrow g}^E$ is low and the frozen-in polarization of the glass is high.

The E -induced free energy of a dipolar liquid would vary with T , according to,

$$\Delta_E G_{liq}(T) = 4.427 \times 10^{-14} [V_m(T) \epsilon_s(T)] E^2 \quad (3)$$

This variation is shown in the illustration in Fig. 1 (bottom panel). The Curie-Weiss equation implicitly takes into account the variation of V_m with T . To consider it separately from variation of ϵ_s , we recall that V_m decreases progressively more slowly on supercooling, but ϵ_s

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