Dielectric Study of Equimolar Acetaminophen–Aspirin, Acetaminophen–Quinidine, and Benzoic Acid–Progesterone Molecular Alloys in the Glass and Ultraviscous States and Their Relevance to Solubility and Stability

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ABSTRACT: Equimolar mixtures of acetaminophen–aspirin, acetaminophen–quinidine, and benzoic acid–progesterone have been vitrified and dielectric properties of their glassy and ultraviscous alloys have been studied. For 20 K/min heating rate, their T_gs are 266, 330, and 263 K, respectively. The relaxation has an asymmetric distribution of times, and the distribution parameter increases with increase in temperature. The dielectric relaxation time varies with T according to the Vogel–Fulcher–Tammann equation, $\log_{10}(\tau_0) = A_{VFT} + [B_{VFT}/(T - T_0)]$, where A_{VFT}, B_{VFT}, and T_0 are empirical constants. The equilibrium permittivity is highest for the aspirin–acetaminophen and lowest for the benzoic acid-progesterone alloy, indicating a substantial interpharmaceutical hydrogen bonding that makes the alloy more stable against crystallization than the pure components. The benzoic acid–progesterone alloy is thermodynamically the most non-ideal. It showed cold crystallization on heating, which is attributed to its relatively greater magnitude of the JG relaxation in relation to its α-relaxation. It is argued that the difference between the free energy of an alloy and the pure components would have an effect on the solubility. Studies of solution thermodynamics of a glassy molecular alloy may be useful for optimizing choice of components and composition to form molecular alloys and to impact drug delivery. J Pharm Sci 99:1358–1374, 2010

Keywords: acetaminophen; aspirin; benzoic acid; progesterone; quinidine; dielectric relaxation; glassy state

INTRODUCTION

Characterization of solid-state properties of amorphous and crystalline pharmaceuticals is of current interest for a variety of reasons. The principal material property amenable to manipulation via formulation approaches has been solubility so that the bioavailability of poorly water-soluble pharmaceuticals can be increased. There are also technical reasons, for example, optimization for controlled delivery, convenience of forming them as tablets, and mechanical stability during transport and storage. Several review articles[1–5] and recent articles[6,7] have described it in detail, which interested readers may consult for an extensive survey of the earlier studies. Bioavailablity, which remains our main

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interest, is limited by both saturation solubility and permeability.

It has been pointed out that at least 25–30% of the compounds in early development have poor bioavailability due to poor solubility,[8] and this accounts for these pharmaceuticals' lack of success during the development process. Thermodynamically, a pharmaceutical in its amorphous state has higher free energy relative to the crystalline state and hence higher solubility. Free energy of materials determines their vapor pressure, and is itself determined not only by the vibrational properties but also by the molecular mobility in a liquid or solid.[9–11] For reasons of practical convenience, free energy is usually estimated from the enthalpy and entropy using classical thermodynamics relations.[9,11] The excess free energy of an amorphous material over the crystal state can also be controlled by the rate at which a liquid is cooled to vitrify it, or as its vapor is deposited, as well as by its thermal history. Thus, it is recognized that controlled enhancement of the free energy of an amorphous pharmaceutical may be used for designing its dosage form. However, calculations based on the heat capacity data have yielded solubility values of amorphous pharmaceuticals that differ considerably from the value obtained from independent measurements of their solubility.[11,12]

The amorphous state is thermodynamically less stable with respect to the crystalline state and therefore amorphous pharmaceuticals can partially or completely crystallize during storage. This reduces their free energy and hence their solubility and bioavailability. It is also kinetically unstable with respect to its own denser state whose free energy (and the fictive temperature, T_f, that is, the temperature at which the glass and melt have the same physical properties) is lower. The decrease in the free energy on spontaneous relaxation of an amorphous structure during storage also decreases its solubility, and this decrease is more if the solid is made by lyophilization, spray drying, vapor-phase deposition, mechanical deformation of crystals or rapid cooling,[13] than when it is made by normal or slower cooling of the melt. (In technical terms, T_f is higher for a glass made by rapid cooling than that made by slow cooling. Thus, solubility decreases as T_f decreases spontaneously.) Lyophilization, spray drying, vapor-phase deposition, mechanical deformation of crystals, and rapid cooling of a melt all produce a glass of higher T_f and higher free energy than the usual slow cooling, and hence produces a state of higher solubility than one made by slow cooling of the melt. Since the solubility ratio of the amorphous to crystalline solid varies with the exponential of the difference between their free energies,[9,11,12] even a small decrease in this difference on structural relaxation causes a relatively large decrease in the solubility ratio. Nevertheless, the effect is much smaller than that of crystallization. Accelerated testing of these occurrences are often performed on amorphous pharmaceuticals,[14] whether they are formed by cooling a melt to the glassy state, by flocculation, lyophilization, or spray drying. Since the properties of an amorphous solid depend upon the production method, thermal history, and storage condition, such accelerated tests would not always lead to information that is reliable in practice. Moreover, a single component, pure amorphous drug produced by lyophilization or vapor-deposition is often physically unstable and slowly crystallizes during storage. Thus, its solubility decreases, partly because a lyophilized state contains minute crystals, which grow during storage or grow after delivery, and partly due to its structural relaxation from an unusually high free energy state. Both decrease the medical specification of the dosage during its shelf life. These practical realities necessitate the development of binary or multi-component glasses in order to stabilize the amorphous pharmaceutical.

The true bioavailability of a relatively insoluble orally administered drug is of course determined not only by the amount dissolved but also by the amount absorbed in the gastrointestinal tract. Therefore, both the enhanced solubility and the time elapsed before its supersaturated solution begins to crystallize[11,12,15] (a process known as solvent-mediated devitrification) determine the efficacy of a pharmaceutical. As part of our studies of producing molecular pharmaceuticals in their glassy state by supercooling of the melt, we have investigated binary alloys of several pharmaceuticals in the glassy and ultraviscous states. These not only have the advantage of forming glasses that are more stable against crystallization than their pure components, but also their melt remains relatively stable without crystallization for a much longer period. A number of earlier studies have provided details of mixed crystals of organic compounds and their phase diagrams[16–19] with some reference to mixed crystals of pharmaceuticals.[17–19] Amorphous solid mixtures of pharmaceuticals with water-soluble polymers and those mixtures that form a colloidal solution have