Dielectric Relaxation and Crystallization of Ultraviscous Melt and Glassy States of Aspirin, Ibuprofen, Progesterone, and Quinidine

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ABSTRACT: Molecular relaxation in ultraviscous melt and glassy states of aspirin, ibuprofen, progesterone, and quinidine has been studied by dielectric spectroscopy. The asymmetric relaxation spectra is characterized by the Kohlrausch distribution parameter of 0.46 ± 0.02 for aspirin to 0.67 ± 0.02 for progesterone. The dielectric relaxation time varies with the temperature, 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 extrapolated τ_0 at calorimetric glass-softening temperature is close to the value expected. The equilibrium permittivity, ε_0, is lowest for ibuprofen which indicates an antiparallel orientation of dipoles in its liquid's hydrogen-bonded structure. A decrease in ε_0 with time shows that ultraviscous aspirin, progesterone, and quinidine begin to cold-crystallize at a relatively lower temperature than ibuprofen. ε_0 of the cold-crystallized phases are, 4.7 for aspirin at 290 K, 2.55 for ibuprofen at 287 K, 2.6 for progesterone at 320 K, and 3.2 for quinidine at 375 K. It is argued that hydrogen-bonding, the Kohlrausch parameter, extent of localized motions and the long-range diffusion times all determine the physical and chemical stability of an amorphous pharmaceutical during storage. J Pharm Sci 96:1159–1175, 2007

Keywords: aspirin; ibuprofen; progesterone; quinidine; molecular relaxation; glassy state

INTRODUCTION

A pharmaceutical's molecule invariably contains hydroxyl, amine, amide or other groups, whose proton donors and acceptor atoms form hydrogen bonds with water, native proteins, fats and carbohydrates. These groups also form intermolecular hydrogen bonds in their liquid, amorphous solid states and, in some cases, in their crystalline states. For technical convenience, Lipinski[1,2] has suggested the Rule of Five (RO5), which has helped provide a considerable recognition to the role of hydrogen-bonding in the small organic molecule pharmaceuticals. Recent literature[3–8] also indicates that physicochemical properties, including those resulting from hydrogen-bonding donor and acceptor abilities of molecules have a significant effect on the molecular diffusion time and its distribution, and hence on solubility and permeability of a pharmaceutical.

The amorphous state of a pharmaceutical is seen as advantageous over the crystalline state not only from the bioavailability consideration,[9–21] but also from the production and packaging consideration. A thermodynamic reason for the first is that the Gibbs free energy minimum of an amorphous solid lies at a higher level than the

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corresponding minimum of the crystalline state. Therefore, for the same size particles, (i) dissolution of an amorphous solid in a solvent occurs with greater decrease in energy than of its crystalline form, (ii) the energy barrier that a molecule in the solid needs to overcome in reaching the solution state is lower for amorphous than for the crystalline state, and (iii) the saturation solubility of the amorphous state is higher. The last of these is expected to increase its bioavailability from the saturated solution state. An ultraviscous melt is also more easily shaped into tablets than the crystalline state thereby providing a technical advantage in processing.

Crystallization and chemical degradation of an amorphous pharmaceutical causes its bioavailability to decrease below the specified value. It also causes minute fractures of the tablet during storage as internal stresses develop on volume change during crystallization. After nucleation of crystal in an ultraviscous melt or an amorphous solid has occurred, further crystal growth results from the ability of molecules to diffuse over a long distance in the disordered structure and, therefore, at high temperatures,[13–15] and/or high humidity[22] conditions, when the molecular diffusion rate is more rapid, crystallization occurs during a shorter time period. This aspect is currently used in discussing crystallization of amorphous pharmaceuticals during storage and in determining their "shelf life."

However, there are several other molecular aspects that add to the ability of an amorphous solid to crystallize, namely, crystal-nucleation and growth occurs at those sites in the amorphous solid structure of molecular pharmaceuticals[23–30] and of certain aqueous proteins[31] where the potential energy is high and where localized molecular motions of the Johari–Goldstein (JG) type occur.[32–36] Based on the general findings of an asymmetric distribution of molecular relaxation times in amorphous solids, Shamblin et al.[37] have suggested that this distribution may also raise the crystal nucleation rate in an amorphous pharmaceutical. Since a distribution of molecular relaxation times and localized molecular motions are characteristic features of an amorphous solid, they have a role in the solid's stability against crystallization and chemical degradation.

We have been experimentally studying the structural relaxation,[38] isothermal and nonisothermal ageing effects,[39] calorimetric relaxation time,[40] phase transformations, electrical conductivity,[41] and dielectric relaxation of pharmaceuticals[42,43] in their ultraviscous melt and glassy states. Here, we report a dielectric relaxation spectroscopy study of molecular motions in the ultraviscous melt and the glassy states of four pharmaceuticals, aspirin, ibuprofen, progesterone, and quinidine, and compare their behavior against that of acetaminophen reported earlier.[42] Except for progesterone which lacks hydrogen bond donors, other pharmaceuticals contain both hydrogen bond donors and acceptors. Our main objective of these studies is to ultimately investigate the role of long-range and localized molecular diffusion as well as that of the distribution of the diffusion times on the rate of cold-crystallization and then finally relate the results to molecule-specific properties. Here, we discuss our results in relevance to pharmaceuticals and neglect their implications for the controversial views on molecular motions in supercooled melts and on the currently debated theories of glass formation. A review of these aspects and their relation to the behavior of another pharmaceutical, acetaminophen, has been provided earlier,[42] which may be consulted.

EXPERIMENTAL METHODS

All pharmaceuticals used were purchased in the purest available form as a fine powder or as granular crystals. Their purities were: aspirin (acetyl salicylic acid) >99%, ibuprofen (2-[4-(2-methylpropyl)phenyl]propanoic acid) >98%, progesterone (17-acetyl-10,13-dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydrocyclopenta-[a]phenanthren-3-one) >98%, and quinidine (2-ethenyl-4-azabicyclo[2.2.2]oct-5-yl)-(6-methoxyquinolin-4-yl-methanol) >98%. Each solid was kept for 30 min at 383 K in an oven in order to remove any moisture. Two calorimeters, (i) Perkin-Elmer Pyris Diamond differential scanning calorimeter (with argon as purge gas) and (ii) TA instruments model Q100 (with nitrogen as purge gas), were used for determining their glass-softening temperature T_g by differential scanning calorimetry (DSC). Both instruments were calibrated prior to use. Platinum pans were used for aspirin, and aluminum pans for the other three. For DSC measurements, the crystalline powder was melted in the calorimeter pan by heating the pan at 10 K/min rate inside the calorimeter and then further keeping it isothermally at a temperature of ~4 K above its melting point for

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