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Recent developments in the experimental investigations of relaxations in pharmaceuticals by dielectric techniques at ambient and elevated pressure☆

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ABSTRACT

In recent years, there is a growing interest in improving the physicochemical stability of amorphous pharmaceutical solids due to their very promising applications to manufacture medicines characterized by a better water solubility, and consequently by a higher dissolution rate than those of their crystalline counterparts. In this review article, we show that the molecular mobility investigated both in the supercooled liquid and glassy states is the crucial factor required to understand molecular mechanisms that govern the physical stability of amorphous drugs. We demonstrate that pharmaceuticals can be thoroughly examined by means of the broadband dielectric spectroscopy, which is a very useful experimental technique to explore different relaxation processes and crystallization kinetics as well. Such studies conducted in the wide temperature and pressure ranges provide data needed in searching correlations between properties of molecular dynamics and crystallization process, which are aimed at developing effective and efficient methods for stabilizing amorphous drugs.

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1. Introduction

Nowadays, many active pharmaceutical ingredients (APIs) are prepared in the crystalline form due to their several advantages. First of all, crystalline pharmaceuticals are thermodynamically stable, and consequently, their physicochemical properties do not change even during

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a long-term storage. Moreover, it is relatively easy to develop repeatable ways of synthesis and analysis of crystalline APIs. Unfortunately, many crystalline drugs are poorly water soluble. This is an extremely disadvantageous feature of crystalline forms of APIs because solubility is one of the most important physicochemical properties in pharmaceutical products' design. The scale of this problem is huge, because more than 75% of drug candidates and 40% of the marketed drugs are poorly soluble in water [1,2], and consequently their bioavailability is strongly limited. A promising way to overcome the drawback is to transform crystalline pharmaceuticals characterized by a long-range translational order to their structurally disordered non-crystalline counterparts (amorphous solids), which may exhibit only a short-range order. The amorphous pharmaceutical solids due to their higher internal energy are often characterized by a better bioavailability than their crystalline counterparts. It is established that solubility and dissolution rate in water are orders of magnitude greater than their crystalline counterparts [3–10]. Unfortunately, the amorphous APIs are thermodynamically unstable systems and may even quickly return to their thermodynamically stable crystalline forms [11–14], which can happen during manufacturing, storage, or dissolution (administration).

To gain a better insight into the physical instability of amorphous drugs, the study of *the glass transition* (from liquid to glass or vice versa) are of special importance. The liquid–glass transition can occur upon isobaric cooling (or under isothermal compression) of a liquid when the time scale of molecular motions responsible for structural rearrangements becomes longer than the time scale of the experiment. As a result, the structural relaxation toward equilibrium is arrested below the glass transition temperature T_g (or above the glass transition pressure P_g) and the system is in the glassy state [15]. This transformation can only be observed if nucleation is suppressed, for example, by sufficiently rapid cooling of a liquid [16]. Investigations of physical phenomena near the glass transition give us valuable information on two states in which the drugs are unstable and can recrystallize, i.e., (*i*) *the glassy state* – a thermodynamically non-equilibrium amorphous solid state and (*ii*) *the supercooled liquid* – a thermodynamically metastable liquid state in the temperature range between T_g and the melting temperature T_m [16,17]. It should be noted that the glass transition and related phenomena are still intensively studied despite more than the half century research in this field. Even the complex nature of the glass transition is continuously under discussion, because the phenomenon falls outside the thermodynamic definitions of the first-order or the second-order phase transitions due to its kinetic character that for instance reflects in the dependence of the glass transition temperature T_g on the experiment (cooling or heating) rate. Nevertheless, a progress of physical, chemical, and material sciences made in this research area [16–20] enabled to develop pharmaceutical studies focused on amorphous APIs. Especially, a lot of effort has been put into better understanding the key factors that govern the recrystallization process in both the supercooled liquid and glassy states as well as finding efficient methods for stabilization of the amorphous forms of drugs.

In order to determine the amorphous solid stability, some thermodynamic properties, e.g., the configurational entropy (S_{conf}), the configurational enthalpy (H_{conf}), and the configurational Gibbs free energy (G_{conf}), have been thoroughly analyzed [21–24]. Among the configurational quantities (considered respectively as the entropic barrier, the enthalpic driving force, and the overall thermodynamic driving force for crystallization), S_{conf} has been found to be useful for predicting the physical stability of amorphous drugs and some correlations have been established between S_{conf} (or H_{conf}) and the tendency of amorphous materials to recrystallization [25,22,26,21]. Nevertheless, it has been realized that the investigations of only the thermodynamic factors are insufficient to completely solve the problems related to the physical stability of amorphous APIs, because the macroscopic thermodynamic quantities do not give us a needed insight into molecular mechanisms that govern the recrystallization process. Therefore, probably the most relevant factor, which should be studied to reliably predict the tendency of amorphous drugs to recrystallization, and consequently, to considerably contribute to the development of the effective and efficient methods for stabilization of the amorphous APIs, is their molecular mobility [27–31,11]. The search for proper correlations between the molecular mobility of amorphous solids and their physical stability is highly complicated, because pharmaceutical materials are often characterized by complex molecular structures of different configurational topologies and a variety of intra- and intermolecular interactions, including specific interactions such as hydrogen bonds of different strengths and electrostatic forces. As a result, the glass-forming pharmaceutical materials usually exhibit complex molecular mobility reflected in several relaxation processes of different natures, which can be distinguished by their properties including their dependence on temperature and pressure. In this context, an important and fervently debated issue is an unambiguous answer to the question: *Which kind of molecular mobility of different time scales, reflected in the structural (global) relaxation associated with the glass transition or different secondary (local) relaxations, can be responsible for the recrystallization of amorphous drugs*?

To study the molecular mobility in both the supercooled liquid and glassy states (in which the time scales of different relaxation processes span an enormously wide range of more than 10 orders of magnitude [32]), the most useful experimental methods are those which enable to explore the complex molecular motions with high resolution in the wide range of their time scales and under different thermodynamic conditions. Although there are several measurement techniques that can be exploited to investigate molecular dynamics (such as nuclear magnetic resonance (NMR), temperature modulated differential scanning calorimetry (TMDSC), thermally stimulated depolarization current (TSDC), quasielastic neutron scattering (QENS), positron annihilation lifetime spectroscopy (PALS), light scattering, and mechanical spectroscopy), the broadband dielectric spectroscopy (BDS) gives us the best possibility to determine time scales of molecular motions of pharmaceuticals in the glassy and liquid states. BDS measurements can be carried out in the wide range of temperatures and pressures over a broad frequency band up to 18 decades (ca. from mHz to THz), which enable to distinguish the global and local molecular motions characterized by their time scales that can change up to 18 orders of magnitude. In addition, the BDS techniques can be easily implemented, because the high quality BDS spectrometers readily available on the market are easy to operate and provide high accuracy experimental data at low costs of measurements (e.g., deuteration of samples is not necessary in contrast to NMR). In recent years, a considerable progress has been made in studies at elevated pressure by means of BDS [19,18,33–37]. It resulted in gaining a better insight into the molecular origin of dielectric relaxation processes near the glass transition as well as the compression effect on the physical stability of amorphous APIs, which is significant for instance during the tableting process [38,12,39–41].

In this review article, we present recent advances in understanding the tendency of amorphous APIs to recrystallization, which have been made with the aim of enhancing the physical stability of amorphous drugs by studying different kinds of molecular mobility in both the supercooled liquid and glassy states at ambient and elevated pressure by means of the BDS techniques.

2. Aspects of the broadband dielectric spectroscopy (BDS) and relaxation processes

The dielectric spectroscopy is based on the interactions of the electric dipole moment and charges of a material sample with an external electric field applied to the sample. This experimental method enables to measure the response of the examined material (polar dielectrics) to the applied alternating electric field $E(\omega)$ in the wide frequency range $f = \omega/2\pi$ ca. from 10^{-5} to 10^{11} Hz (which can be extended to about 10^{13} Hz by employing THz measurement techniques). As a result, in the frequency domain, one can explore the following phenomena occurring in the sample [42]: