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The Slow Relaxation Dynamics in the Amorphous Pharmaceutical Drugs Cimetidine, Nizatidine, and Famotidine

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ABSTRACT

The slow molecular mobility in the amorphous solid state of 3 active pharmaceutical drugs (cimetidine, nizatidine, and famotidine) has been studied using differential scanning calorimetry and the 2 dielectric-related techniques of dielectric relaxation spectroscopy and thermally stimulated depolarization currents. The glass-forming ability, the glass stability, and the tendency for crystallization from the equilibrium melt were investigated by differential scanning calorimetry, which also provided the characterization of the main relaxation of the 3 glass formers. The chemical instability of famotidine at the melting temperature and above it prevented the preparation of the amorphous for dielectric studies. In contrast, for cimetidine and nizatidine, the dielectric study yielded the main kinetic features of the α relaxation and of the secondary relaxations. According to the obtained results, nizatidine displays the higher fragility index of the 3 studied glass-forming drugs. The thermally stimulated depolarization current technique has proved useful to identify the Johari–Goldstein relaxation and to measure $\tau_{\beta JG}$ in the amorphous solid state, that is, in a frequency range which is not easily accessible by dielectric relaxation spectroscopy.

Introduction

The vast majority of modern active pharmaceutical ingredients (APIs) are made up of complex molecules with very low water solubility in their most stable crystalline state. The fact that the amorphous solid drugs are in a higher energy state compared to their crystalline counterparts gives them a higher solubility and a faster dissolution rate, which leads to a higher bioavailability. It is thus in the best interest to take advantage of this behavior in the formulation of poorly water-soluble drugs.[1-5] The use of APIs in the amorphous solid state is however limited by the glass instability (tendency to crystallization). The stability of the amorphous solid form of a drug greatly varies from substance to substance. Furthermore, the stability of an amorphous solid depends on the amorphization method (melt quenching, freeze drying, ball milling, cryomilling).[6,7] A close relationship seems to exist between molecular mobility and chemical and physical stability of the amorphous.[8,9] In fact, the cooperative mobility was found to be responsible for instability,[9,10] and correlations were found between the relaxation time of the α relaxation and the crystallization onset time in amorphous pharmaceuticals.[11] It was also shown that the Johari–Goldstein relaxation can facilitate the main mobility even if it is not directly the cause of the amorphous instability.[8] The importance of the local mobility in determining the chemical stability of macromolecules was highlighted,[12-15] and there is also slight evidence about the destabilizing role of the fast secondary motions.[16] These fast secondary motions probably also contribute to instability in situations such as the crystallization of amorphous indomethacin and celecoxib, which may occur at several tens of degrees below the glass transition temperature, T_g, conditions where molecular diffusion is too restricted for nucleation and crystal growth to take place.[17,18] Some recent works are valuable contributions to the understanding of the relationship between molecular mobility, glass-forming ability, and glass stability.[19,20]

When the amorphous drug is unstable, stabilization of the glassy form is important to take advantage of the solubility and bioavailability benefits of the amorphous state. Stabilizing an amorphous API is achieved by obtaining a glassy mixture of the API in a polymer matrix (the amorphous solid dispersion)[21-24] or through the so-called coamorphous mixtures.[25-27] In any event, understanding the molecular mobility in the pure API and in the

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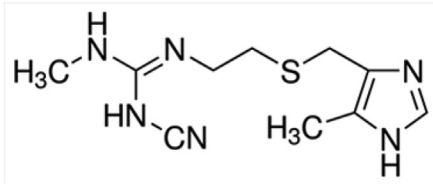
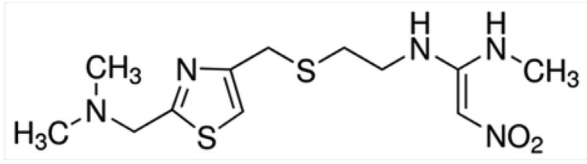
mixtures is important for finding the best stabilization method and for designing the most appropriate mixtures.

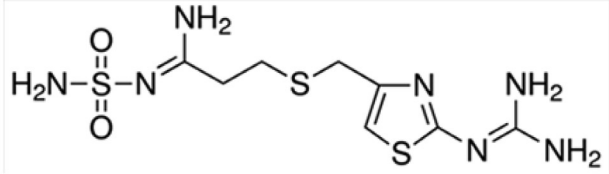
This work is a study by differential scanning calorimetry (DSC), thermally stimulated depolarization currents (TSDC), and dielectric relaxation spectroscopy (DRS) of the slow molecular mobility in the amorphous solid state of 3 APIs: cimetidine,[28] nizatidine,[29] and famotidine.[30] These are H2 antagonists or H2 blockers, a class of medications that block the action of histamine at the histamine H2 receptors of the parietal cells in the stomach, decreasing the production of stomach acid. They are also used to treat peptic ulcer disease, gastroesophageal reflux disease, and hypersecretory syndromes such as the Zollinger–Ellison syndrome. In addition, these drugs are currently being considered for alternative indications. We will use DSC first to characterize the thermal behavior: glass transition, melting, crystallization, glass-forming ability, glass stability, and tendency for crystallization on cooling from the equilibrium melt. Then, we will use DSC to characterize the structural relaxation of the 3 drugs. With TSDC and DRS, we will analyze the slow molecular mobility in the amorphous solid form of cimetidine and nizatidine; the decomposition of famotidine that occurs very close to the melting point makes difficult the production of the glass by quench cooling from the melt, which prevented the dielectric study of this substance. The 2 dielectric techniques provide quantitative and complementary information on the distribution of relaxation times of the different slow motional modes. In fact, although the low equivalent frequency of TSDC leads to an enhancement of the resolution power of the different relaxations, the very wide frequency range of DRS constitutes an enormous advantage of this experimental technique. DRS is unanimously considered as a powerful technique for the study of molecular mobility in glass-forming substances. On the other hand, an important advantage of TSDC is the possibility, using the partial polarization (PP) procedure (see Experiments section), to experimentally resolve a broadly distributed relaxation process into its narrowly distributed components; this enables the calculation of the temperature-dependent relaxation time, $\tau(T)$, associated to individual or very narrowly distributed motional modes. These are reasons, among others, that make TSDC and DRS very useful complementary tools for slow molecular dynamic studies.



Cimetidine



Nizatidine



Famotidine

Figure 1. The chemical structures of cimetidine, nizatidine, and famotidine.

Experiments

Materials

Cimetidine, empirical formula $C_{10}H_{16}N_6S$, CAS number: 51481-61-9, molar weight M_w = 252.34 g/mol, was purchased from TCI (purity > 99%); the melting temperature, taken as the endothermic peak's maximum, was found to be T_{fus} = 143.1°C, in agreement with published values in the literature,[31-35] and the melting enthalpy was determined as ΔH_{fus} = 40.4 kJ/mol, compared to the published value of ΔH_{fus} = 35.2 kJ/mol.[33]

Nizatidine, empirical formula $C_{12}H_{21}N_5O_2S_2$, CAS number: 76963-41-2, molar weight M_w = 331.46 g/mol, was purchased from TCI (purity > 97%); the melting temperature was found to be T_{fus} = 132.5°C, in agreement with published values in the literature,[31,36,37] and the melting enthalpy was determined as ΔH_{fus} = 36.9 kJ/mol, compared to the published value of ΔH_{fus} = 45 kJ/mol.[36]

Famotidine, empirical formula $C_8H_{15}N_7O_2S_3$, CAS number: 76824-35-6, molar weight M_w = 337.45 g/mol, was purchased from TCI (purity > 98%); the melting temperature was found to be T_{fus} = 165.5°C, in agreement with values published in the literature,[31,37-39] and the melting enthalpy was determined as ΔH_{fus} = 47.4 kJ/mol, compared to the published values ΔH_{fus} = 43.5,[40] 49.9,[39] 50.6,[41] 51.3,[42] and 55.4 kJ/mol.[38]

These substances were used without further purification. The chemical structures are shown in Figure 1.

Techniques

Differential Scanning Calorimetry

The calorimetric measurements were performed with a 2920 MDSC system from TA Instruments Inc. The samples of ~5-10 mg were introduced in aluminum pans. The measuring cell was continuously purged with high purity helium gas at 30 mL/min. An empty aluminum pan, identical to that used for the sample, was used as the reference. Details of the calibration procedures are given elsewhere.[43]

Thermally Stimulated Depolarization Currents

TSDC experiments were carried out with a TSC/RMA spectrometer (TherMold, Stamford, CT) covering the range from −170°C to 400°C. For TSDC measurements, the sample (thickness of ~0.5 mm) was placed between the disc-shaped electrodes (7 mm diameter) of a parallel plane capacitor and immersed in an atmosphere of high purity helium (1.1 bar).