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Research paper

Thermodynamic behavior of glassy state of structurally related compounds

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Abstract

Thermodynamic properties of amorphous pharmaceutical forms are responsible for enhanced solubility as well as poor physical stability. The present study was designed to investigate the differences in thermodynamic parameters arising out of disparate molecular structures and associations for four structurally related pharmaceutical compounds – celecoxib, valdecoxib, rofecoxib, and etoricoxib. Conventional and modulated temperature differential scanning calorimetry were employed to study glass forming ability and thermodynamic behavior of the glassy state of model compounds. Glass transition temperature of four glassy compounds was in a close range of 327.6–331.8 K, however, other thermodynamic parameters varied considerably. Kauzmann temperature, strength parameter and fragility parameter showed rofecoxib glass to be most fragile of the four compounds. Glass forming ability of the compounds fared similar in the critical cooling rate experiments, suggesting that different factors were determining the glass forming ability and subsequent behavior of the compounds in glassy state. A comprehensive understanding of such thermodynamic facets of amorphous form would help in rationalizing the approaches towards development of stable glassy pharmaceuticals.

Keywords: Differential scanning calorimetry; Amorphous; Glass transition temperature; Fragility; Heat capacity

1. Introduction

From a pharmaceutical perspective, the interest in the amorphous state stems from its higher apparent solubility and dissolution rate as compared to crystalline counterparts [1]. However, the excess properties [2] of enthalpy, entropy and free energy, that endow the desirable property of high solubility, are also responsible for the devitrification tendency of the amorphous systems. Despite numerous studies on amorphous systems, the reach of these systems to the market has been abysmal. This failure can at least in part be attributed to the incomplete understanding of these systems and lack of confidence in their behavior. Thereby, a fundamental understanding of the physicochemical properties of the amorphous state is necessary to develop products with consistent performance.

An investigation of the molecular and thermodynamic factors responsible for the differential behavior of the pharmaceutical amorphous systems is of paramount importance. This is not only likely to lead to a better understanding of the amorphous phase but may also provide leads for rational stabilization strategies for amorphous systems. A number of studies have reported a comparative assessment of the thermodynamic properties of amorphous phases of diverse compounds [3–7]. Zhou et al. related the physical stability of the compounds to configurational thermodynamic quantities and molecular mobility [7]. Shamblin et al. reported the effect of aging and the method of amorphous phase preparation on the thermodynamic properties of sorbitol, sucrose, trehalose, and indomethacin. These studies underscored the

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importance of inherent thermodynamic differences in determining the macroscopic behavior of the investigated compounds. However, most of these studies compared molecules differing to a relatively large extent in their molecular weight, and chemistry. Consequently, these compounds differed with respect to the 'start up' property of glass transition temperature (T_g). Since T_g is the foremost property of amorphous solids, compounds with diverse T_g's will more likely than not present different thermodynamic behavior. Hence, there exists a need to systematically examine the thermal behavior of amorphous phase of structurally similar compounds with comparable T_gs.

The present study was designed to address this issue by taking up a series of structurally related compounds for investigation of their thermodynamic properties. The objective was to investigate the differences in thermodynamic parameters arising out of disparate molecular structures and associations. Four structurally related compounds providing both a sufficient degree of similarity and diversity in their structure – celecoxib, valdecoxib, rofecoxib, and etoricoxib – were chosen as model compounds for the study.

2. Materials and methods

2.1. Materials

Celecoxib (Unichem Laboratories, Mumbai, India), valdecoxib (Aarti Drugs, Mumbai, India), rofecoxib (Ranbaxy Research Laboratories, Gurgaon, India), and etoricoxib (Aarti Drugs, Mumbai, India) were each of >99.9% assay value and were used as received. Calibration standards – gallium (Sigma–Aldrich Co., St. Louis, MO, USA), tin (Sigma–Aldrich Co., St. Louis, MO, USA), indium (Mettler Toledo, Schwerzenbach, Switzerland), and sapphire (Mettler Toledo, Schwerzenbach, Switzerland) were used to calibrate the differential scanning calorimeter (DSC) for enthalpy and temperature.

2.2. Preparation of amorphous forms

Amorphous forms were prepared by heating crystalline drug (3–5 mg) in DSC in a pin-holed aluminum pan to a temperature of about 20 K above the respective melting points, holding for 1 min, and then immediately cooling to 298 K at 20 K/min. The high-performance liquid chromatography assay of the amorphous samples established that no degradation occurred during the preparation of amorphous forms.

2.3. Differential scanning calorimetry

Conventional and modulated temperature (MT) DSC experiments were performed on Mettler Toledo DSC 821^e (Mettler Toledo, Switzerland) instrument, operating with STAR^e software version 5.1, and equipped with an intracooler. The samples (3–5 mg) were analyzed under dry nitrogen purge (80 ml/min) in crimped and pin-holed aluminum pans. Crystalline and amorphous samples were scanned at a rate of 20 K/min over a temperature range of 298 K to well above the respective melting points. The DSC instrument was calibrated for temperature and heat flow using high-purity standards of gallium, indium, and tin. The heat capacity constant was calibrated using a sapphire disc. All DSC measurements were done in triplicate.

2.4. Heat capacity measurements

Modulated temperature DSC (MTDSC) is one of the most acceptable techniques for the measurement of heat capacity at constant pressure (C_p) of crystalline and amorphous pharmaceuticals. However, numerous experimental conditions such as – modulation parameters, purge gas, sample geometry, pan type, and calibration status should be optimized to avoid erroneous results. Helium gas is usually preferred due to its superior thermal conductivity and thereby its ability to afford aggressive modulation. However, due to this very property of helium, it is likely to cause errors because of high sensitivity caused by even subtle changes in gas flow. In the absence of requirement for aggressive modulation and availability of conventional gas flow control valves, nitrogen gas at a flow rate of 80 ml/min was found to be adequate for heat capacity measurements by MTDSC. The modulation parameters for heat capacity measurements were – modulation period of 60 s, amplitude of ±0.3 K, and an underlying heating rate of 0.9 K/min. Samples weighing about 3–5 mg were compressed into discs and encapsulated in standard aluminum pans, crimped, and pin holed. Sample preparation and encapsulation was done to ensure a good sample to pan contact facilitating heat transfer during modulation. Loose powders, especially micronized powders, contain a lot of air, which leads to an underestimation of heat capacity. Therefore, flat discs that ensure good contact at the bottom of the crucible were utilized for MTDSC. Moreover, to match the sample geometry of the amorphous sample (that was formed as a glassy disc upon cooling of the melt), the crystalline sample was compacted. Amorphous samples were prepared from the same crystalline sample *in situ*, and MTDSC of the glassy sample was carried out in a subsequent run. The sample and reference pans weights were matched to within 20 mcg to minimize background heat capacities. As per the manufacturer's recommendation, the DSC cell was 'burned in' (heated to a temperature of 500 °C for 10 min) to maximize sensitivity. MTDSC measurement involved the running of 'blank', 'calibration', and 'sample' runs. Measurement was done over a range of 313–343 K, encompassing the glass transition range for the four compounds. Heat capacity was calculated by deconvolution, using commercial software 'ADSC C_p'. Heat capacity jump at T_g was measured for amorphous samples. Each heat capacity measurement was repeated thrice and arithmetic mean was used for calculations. Relative standard deviation was typically less than 3%.