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Physico-Chemical Characterization and Stability Study of Glassy Simvastatin

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ABSTRACT The objective of the present study was to investigate the glass forming capability of a model drug simvastatin. The glassy material produced by melt quench technique was subjected to physico-chemical characterization and subsequent stability and enthalpy relaxation study. The chemical stability of drug during preparation of glass was tested by High Performance Liquid Chromatography (HPLC) and Infrared (IR) spectroscopy. The presence of amorphous form was confirmed by DSC and XRPD. Surprisingly, glassy simvastatin was almost stable throughout the period of stability, inspite of its T_g being relatively low. The stability and very low enthalpy recovery of glassy simvastatin perhaps could be attributed to strong inter-molecular hydrogen bonding.

KEYWORDS Simvastatin, Amorphous, Stability, Enthalpy relaxation

INTRODUCTION

Over the last few years, there has been growing awareness regarding importance of the glassy state in pharmaceutical products (Hancock & Zografi, 1997; Lian, 2001). A glass is defined as an amorphous solid that exhibits glass transition (T_g), which is a phenomenon by which the solid amorphous exhibits an abrupt change in derivative thermodynamic properties (e.g., heat capacity or thermal expansivity) with a change in temperature (Hilden & Morris, 2004). Amorphous solids lack the three-dimensional long-range order found in crystalline solids and the position of the molecules relative to one another is more random, as in the liquid state. The high internal energy and specific volume of the amorphous state relative to the crystalline state can create the possibility of its spontaneous conversion back to the more stable crystalline state during processing or storage. In general, the stability of amorphous materials can be improved by storage well below the T_g (Hancock & Zografi, 1994) and by protection from plasticizer (e.g., water vapor), which can depress the T_g to below the storage temperature during stability (Shalaev & Zografi, 1996; Zografi, 1988).

The most common techniques for producing an amorphous phase in pharmaceutical systems include mechanical activation of crystalline mass (e.g.,

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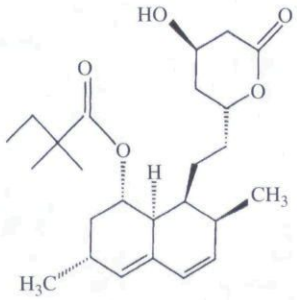

FIGURE 1 Chemical Structure of SIM.

milling), rapid precipitation from solution, and continuous concentration processes (e.g., freeze-drying or spray-drying). However, the technique employed on the laboratory scale is quench-cooling of a melt. Although this technique is not used for large-scale production of pharmaceutical products, it is often employed as a first approach for preparing the amorphous phase of a compound.

The objective of the present study was to investigate the glass forming capability of a model drug simvastatin (SIM), which is a cholesterol-lowering agent widely used to treat hypercholesterolemia. The chemical structure of SIM is shown in Fig. 1. The glassy material produced by melt quench technique was subjected to physico-chemical characterization and subsequent stability and enthalpy relaxation study.

EXPERIMENTAL

Materials

SIM was a generous gift from IVAX India Pvt. Ltd. (Mumbai, India). All other chemicals and solvents were of reagent grade.

Methods

Preparation of Glassy SIM

SIM crystals were melted in a beaker by heating on a paraffin oil bath maintained at 150°C. The melt was immediately solidified by cooling on an ice bath. The solidified melt (glass) formed was stored in desiccated environment until further study.

HPLC Analysis

During preparation of glass, the chemical stability of SIM was tested by HPLC. The system specifications were: Pump: PU-1580, JASCO, Japan; Injector: auto sampler (AS-1555, JASCO, Japan); Column: RP C18, 250 × 4.6 mm (Kromasil® 100, 5 μm, Flexit Jour Lab. Pvt. Ltd., Pune, India); Detector: UV/Visible (UV-1575, JASCO, Japan). Data acquisition and analysis was carried out using Borwin/HSS 2000 software (LG 1580-04, JASCO, Japan). The chromatographic conditions were as follows: Mobile phase: acetonitrile:-methanol (95:5); Flow rate: 1 ml/min; Wavelength: 238 nm.

Infrared (IR) Spectroscopy

Infrared (IR) spectroscopy was performed on Fourier transformed-infrared spectrophotometer (V 5300, JASCO, Japan). The pellets of drug and KBr were prepared on KBr-press (Spectra Lab., India). The spectra were scanned over wave number range of 4000 to 400 cm^{-1}.

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) studies were carried out using Mettler-Toledo DSC 821^e instrument equipped with an intracooler (Mettler-Toledo, Switzerland). Indium/zinc standards were used to calibrate the DSC temperature and enthalpy scale. The samples were hermetically sealed in aluminum pans and heated at a constant rate of 20°C/min over a temperature range of 20–150°C. Inert atmosphere was maintained by purging nitrogen gas at flow rate of 50 mL/min.

X-Ray Powder Diffraction (XRPD)

The XRPD patterns were recorded on X-ray Diffractometer (PW 1729, Philips, Netherlands). The samples were irradiated with monochromatized CuKα radiation (1.542 Å) and analyzed between 2 to 50°2θ. The voltage and current used were 30 kV and 30 mA, respectively. The range and the chart speed were 5×10^3 CPS and 10 mm/°2θ, respectively.

Stability Study

The stability of glassy SIM was monitored up to 6-months at 25°C/60%RH. Periodically (initially 1-month, 3-months, and 6-months) samples were removed and characterized by DSC and XRPD studies for presence of crystallinity.

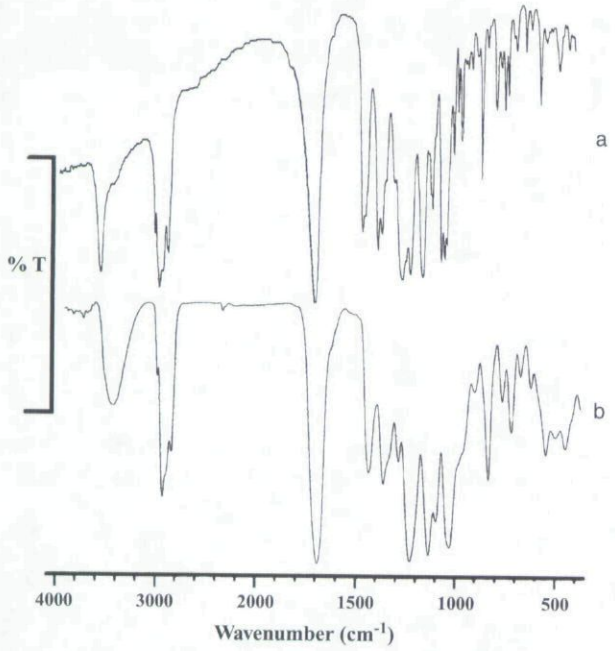

FIGURE 2 IR Spectral Data for Different Samples of SIM. Key: Crystalline SIM, (a); Glassy SIM, (b).

Enthalpy Relaxation Study

The enthalpy relaxation studies to support the stability data were carried out as per the method reported previously (Ambike et al., 2004). The instrumental specifications and operational parameters were similar as stated earlier with only a few modifications in the heating and cooling cycles, which were as follows: In the first cycle, samples were heated 3°C above the melting temperature of SIM at a constant rate of 20°C/min and maintained at that temperature for about 1 min to standardize the thermal history. The samples were then cooled immediately in DSC instrument itself up to 20°C, at a constant rate of −20°C/min, to generate the amorphous form. In the subsequent heating cycle, the pronounced endothermic recovery peak, located at the end of the glass transition region, was analyzed. The samples were aged at 25°C/60%RH for specified time period (16 h) and analyzed periodically (initially 2, 4, 8, and 16 h) for enthalpy relaxation at T_g. Each time the heating run was continued until melting temperature of SIM to confirm any incidence of crystallization.

RESULTS AND DISCUSSION

The solidified melt of SIM appeared as a transparent and brittle glassy mass. Both crystalline and glassy samples gave a single peak with the same retention time in HPLC analysis, indicating no decomposition of the drug during melting process.

IR Spectroscopy

IR spectra of crystalline SIM (Fig. 2a) presented characteristic peaks at 3553, 2964, and 1714 cm^{-1}, which could be attributed to free O–H stretching vibrations, C–H stretching vibrations and stretching vibrations of ester and lactone carbonyl functional group, respectively. Glassy SIM (Fig. 2b) presented significant shift and broadening in O–H stretching vibrations (3460 cm^{-1}), suggesting the possibility of inter-molecular hydrogen bonding. Whereas the low frequency region (1000–400 cm^{-1}) of both the spectra was almost unchanged, overall symmetry of the molecule is not significantly affected even though the drug is in the amorphous phase.

DSC and XRPD Studies

DSC thermogram of crystalline SIM (Fig. 3a) showed a sharp endotherm at 139°C (ΔH 77.4 J/g) attributed to its melting. Similarly, its XRPD (Fig. 4a) presented prominent diffraction peaks in the range of 8–32°2θ. On the other hand, the thermogram of glassy SIM (Fig. 3b) did not show the melting transition; instead, a T_g appeared at 35°C. This clearly indicated the existence of amorphous state of the drug, which was also confirmed by XRPD (Fig. 4b) showing a halo, characteristic to amorphous form.

Stability and Enthalpy Relaxation Studies

During stability, the DSC observations at the end of 1-month (Fig. 3c) were almost identical with the

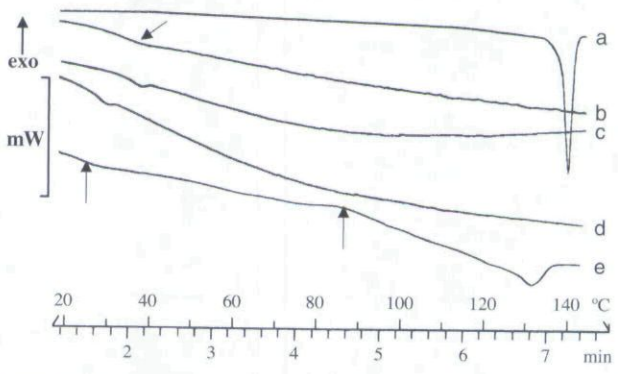

FIGURE 3 DSC Data for Different Samples of SIM. Key: Crystalline SIM, (a); Glassy SIM-Initial, (b); Glassy SIM 1-Month, (c); Glassy SIM 3-Months, (d); Glassy SIM 6-Months, (e).

initial observations with decrease in T_g from 35°C to 33°C. After 3 months of storage (Fig. 3d), there was further decrease in T_g from 33°C to 27°C, without any incidence of crystallinity. However, at the end of 6 months of storage (Fig. 3e), T_g further decreased to 25°C, along with appearance of a broad exotherm at around 84°C (ΔH 4.81 J/g), possibly due to recrystallization of amorphous form, which was followed by an endotherm at around 134°C (ΔH 25.36 J/g) indicating melting transition of recrystallized fraction of drug sample. The XRPD data (Fig. 4c–e) also supported the observations of DSC. Even though the characteristic peaks of drug were absent through out the period stability, there was significant elevation of the diffractogram after 6 months of storage.

The stability of glassy SIM could also be explained on the basis of enthalpy relaxation studies (Matsumoto & Zografi, 1999; Shamblin & Zografi, 1998). Amorphous substances aging at a temperature below T_g show crystallization of glassy state via the equilibrium supercooled liquid state. The material experiences gradual loss in energy in terms of enthalpy because of the effect of molecular motions occurring at prevailing conditions, which drive it towards a more stable crystalline state. This loss of enthalpy is recovered by the sample at T_g during its heating run in DSC and can be measured with time. The glassy SIM aged at 25°C/60%RH for 16 h presented no incidence of crystallinity (Fig. 5a–e), but there was a very slight decrease in T_g from 35°C to 34°C at the end of 4 h. At the end of 16 h there was no further

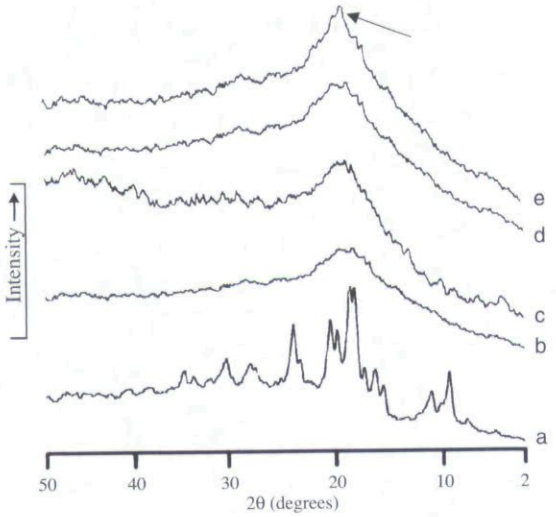

FIGURE 4 XRPD Data for Different Samples of SIM. Key: Crystalline SIM, (a); Glassy SIM-Initial, (b); Glassy SIM 1-Month, (c); Glassy SIM 3-Months, (d); Glassy SIM 6-Months, (e).

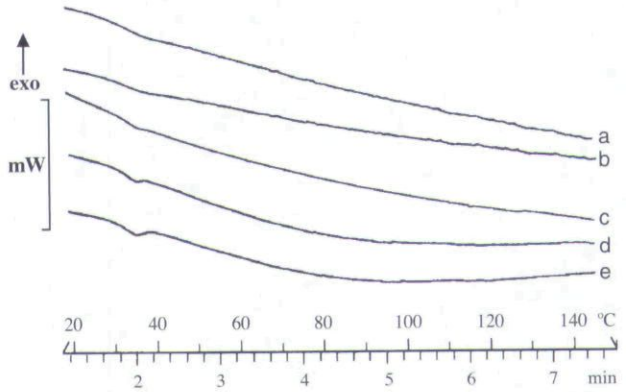

FIGURE 5 Enthalpy relaxation study of glassy SIM at different time intervals. Key: initial, (a); 2 h, (b); 4 h, (c); 8 h, (d); 16 h, (e).

decrease in T_g, but the size of endothermic peak accompanying T_g experienced slight enhancement reflecting an increase in enthalpy recovery and structural relaxation of amorphous form towards the supercooled liquid region.

CONCLUSION

The present study demonstrated that crystalline SIM could be physically transformed to its amorphous form without any chemical degradation. Initial characterization by DSC and XRPD studies confirmed the presence of amorphous form. Surprisingly, glassy SIM was almost stable throughout the period of stability inspite of its T_g being relatively lower (35°C). The stability and very low enthalpy recovery of glassy SIM perhaps could be attributed to strong inter-molecular hydrogen bonding as indicated by IR spectroscopy. The study thus definitely reveals tremendous potential of glassy SIM from the formulation point of view.

ACKNOWLEDGMENTS

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