J. Pharm. Pharmacol. 1986, 38: 219–220
Communicated August 12, 1985

Effect of thermal history on the glassy state of indapamide

ABU T. M. SERAJUDDIN*, MORTON ROSOFF†, DANIEL MUFSON‡, *Pharmacy R & D Department, Revlon Health Care Research, Tuckahoe, New York 10707, USA*

The effects of thermal history, e.g. cooling rate, annealing, etc., on the thermal behaviour of indapamide glass were determined by differential scanning calorimetry (DSC). The glass was prepared by heating indapamide crystals (m.p. 162 °C) to 180 °C, and then cooling the melt to room temperature. The glass transition temperature (T_g) of the material was 98 °C. An endotherm, due to thermal relaxation of the glass, was observed in the DSC thermogram when indapamide glass was prepared by slow cooling or was annealed isothermally at a temperature below T_g. Such enthalpy relaxation may be observed during ageing of pharmaceutical glasses and might influence their physicochemical properties.

Glasses are traditionally defined as amorphous solid bodies formed by continuous hardening or solidification of a liquid (Chaudhari & Turnbull 1978). Many medicinal agents can exist in glassy states when cooled after melting (Kuhnert-Brandstätter 1971), and there has been a great interest within the pharmaceutical field in glassy and amorphous states of drugs and excipients in dosage form design (Mullins & Macek 1960; Chiou & Riegelman 1969; Summers & Enever 1976; Black & Lovering 1977; Timko & Lordi 1984). It has been shown that the thermal history, e.g. cooling rate, annealing, etc., has major effects on thermal properties of the glassy states of polymers (Wunderlich 1964; Petrie 1972; Chen et al 1980); these changes were related to the enthalpy relaxation of glassy polymers. However, there has been no study on the effects of thermal history of the glassy states of drugs and excipients on their thermal properties. Since most of these materials have much lower molecular weight than polymers and do not generally have chainlike and/or coiled structures, it is of interest to study whether they undergo enthalpy relaxation similar to polymers. In the present report, the effect of thermal history on the glassy state of indapamide, a diuretic antihypertensive of relatively low molecular weight (365·8), is described.

Materials and methods

The indapamide used was manufactured in crystalline form by USV Laboratories, Tarrytown, N.Y. The crystals (m.p. 162 °C) were heated to 180 °C at a rate of 3 °C min^{-1} by placing a sample on a microscopic slide within the microfurnace of a Mettler FP5 hot stage. Cooling the melt to ambient temperature formed indapamide glass. To study the effect of cooling rate on the glass formed, the melt was cooled by quenching by placing the slide on a cold metallic plate (10 °C), or it was cooled at a particular rate by keeping the slide inside the microfurnace. The thin layer chromatography of the glass showed no significant degradation of indapamide. The microscopic study using polarized light confirmed that all crystals melted at 180 °C, and no crystalline form remained in the glass. The nature of the glass did not change if the crystals had been heated beyond 180 °C; however, some degradation of indapamide was observed if the temperature exeeded 200 °C during the preparation of glass. The formation of glass was also not dependent on the mode of heating; glass was formed when the crystalline material was heated by other methods, e.g. oil bath, differential scanning calorimetric (DSC) cell, and then cooled. The indapamide glass remains stable under anhydrous conditions, no endotherm having been observed in the melting range of its crystalline form for at least 2 years. However, it converts to the original crystalline form in the presence of moisture or water.

The thermograms of indapamide glasses prepared at different cooling rates were recorded by using a DuPont 990 thermal analyzer. For this purpose, 4 mg of a sample was heated from 25 to 200 °C in a crimped aluminium pan at a rate of 10 °C min^{-1}. To evaluate the effect of isothermal annealing, a sample of the glass prepared by quenching was stored in an oven at 85 ± 1 °C.

Results and discussion

The effect of the rate of cooling of a melt of indapamide crystals on the thermal properties of the glass formed is shown in Fig. 1. The glass transition temperature, T_g, of the material was observed to be 98 °C. No endotherm at T_g was evident following quenching of the sample. However, when the melts were allowed to cool slowly inside the hot stage microfurnace, an endotherm was observed at T_g. The size of the endotherm increased with a decrease in cooling rate during glass formation. Petrie (1972) reported that, with glassy states of polymers, the formation of an endotherm at T_g is due to annealing. It is, therefore, possible that the endotherms in Fig. 1 are also due to annealing during the cooling process. The thermograms of the samples annealed isothermally for different periods of time at a temperature below T_g (Fig. 2) confirms this effect. The area over the endotherm increases with the annealing time and reaches its maximum in 168 h.

When a liquid becomes a glassy solid on cooling

* Correspondence.
Present addresses: † Arnold and Marie Schwartz College of Pharmacy and Health Sciences, Brooklyn, NY 11201 and ‡ Liposome Technology, Inc., Menlo Park, CA 94025, USA.

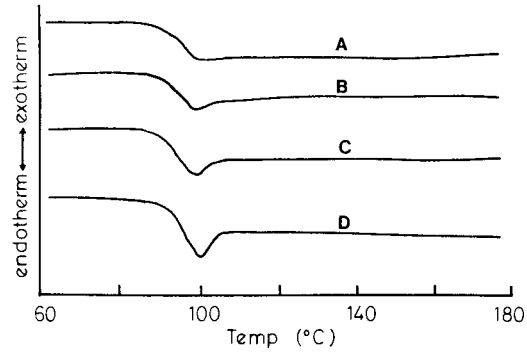

FIG. 1. The DSC thermograms of indapamide glass showing the effect of cooling rate during the preparation of the glass on the size of endotherm at the glass transition temperature. Key: Cooling rate, A, quenching; B, 10 °C; C, 3 °C; and D, 1 °C min^{-1}.

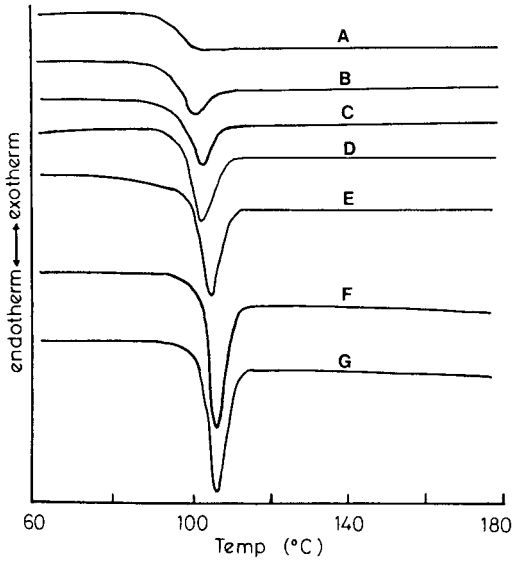

FIG. 2. The DSC thermograms of indapamide glass showing the effect of the duration of annealing at 85 °C on the size of endotherm at the glass transition temperature. Key: Annealing time, A, 0; B, 2; C, 4; D, 21; E, 45; F, 168; and G, 336 h.

through the glass transition temperature, large-scale molecular motion is frozen without a change in structure. A glassy material formed by quenching or under normal atmospheric cooling conditions, therefore, has an excess of enthalpy relative to the corresponding equilibrium glassy state. It reaches equilibrium during annealing by enthalpy relaxation (Petrie 1972), that is, by releasing the strain produced by rapid cooling. Theoretical calculations (Petrie 1972) showed that the absorption of thermal energy in the glass transition interval during the heating cycle of an annealed glass, corresponds to the enthalpy relaxation during annealing. For a particular annealing temperature, T_A, the maximum relaxation of enthalpy, that is, the difference between the enthalpy of the unannealed glass and the enthalpy of glass under equilibrium conditions, is equivalent to $(C_f - C_g)(T_g - T_A)$, where C_f and C_g are the specific heats of fluid and glass, respectively. Thus, the maximum relaxation of enthalpy due to annealing at a particular temperature can be calculated theoretically if specific heats are known. It may also be determined from the area of the maximum endotherm as shown in Fig. 2.

The results of the present investigation indicate that glassy forms of low molecular weight organic molecules may be susceptible to annealing. Similar studies may be helpful in the analysis of possible changes in thermograms during the ageing of pharmaceutical glasses. Only the glass → crystal conversion was investigated in earlier studies on the ageing of low molecular weight pharmaceutical glasses (Ford & Rubinstein 1977) and no consideration was given to annealing. It is also interesting to inquire whether pharmaceutical glasses with energies dependent on their thermal history may be analagous to polymorphism in the crystalline state, and would have differences in physico-mechanical properties, dissolution rates and bioavailability.

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