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Some physicochemical properties of glassy felodipine

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Summary

Felodipine, a normally crystalline and very slightly soluble Ca-antagonist was prepared in glassy form and some of its physicochemical properties were determined. The glassy state was confirmed by X-ray diffraction method, scanning electron microscopy (SEM) and differential scanning calorimetry (DSC). The influence of the cooling rate of the melt and the heating rate of the glass formed on the glass transition temperature was examined. The jump of the heat capacity, the area under the anomalous endothermic peak and the activation energy of the glass transition were calculated. The influence of the heating rate of the glassy felodipine on its crystallization was studied and the kinetic data of the crystallization were obtained. Dissolution tests were carried out and differences were established.

Introduction

The glassy state may improve bioavailability of drugs if it increases the dissolution rate and hence the absorption of drugs. There have been numerous reports on the glassy state of high-molecular compounds, but the nature of the glassy state of low-molecular compounds has been less well investigated. The glass behaviour and glass properties of some pure low-molecular-weight compounds have been investigated thermodynamically (Suga and Seki, 1974; Haida et al., 1977).

Several drugs have been reported to form glasses with citric acid, and various barbiturates have also been reported to be capable of the glass formation (Chiou and Riegelman, 1971; Summers, 1978). However, the description of the glass transition process and the glassy state are more or less empirical in nature. The properties of solids formed by cooling the melts have been reported by several authors (Borka, 1974; Ford and Rubinstein, 1978; Imaizumi et al., 1980). Borka (1974) reported that indomethacin solidified after melting as a brittle, glassy amorphous mass which remained uncrystallized for at least two months at room temperature.

Well-established methods to study the kinetics of reactions are based on the determination of the amount of reactant decomposed after various time intervals. These experiments are usually carried out isothermally at a range of temperatures and are therefore rather time-consuming (Kerč et al.,

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1989). The DSC technique has the advantage of being very rapid and versatile. A single, temperature programmed DSC experiment can be used to compute the Arrhenius preexponential factor, A, activation energy, E_a, and order of the reaction, n, (Schlichenmaier and Widmann, 1977).

However, there is much confusion in the literature about the kinetic constants obtained through DSC experiments (Ford and Timmuns, 1989). Large discrepancies were found between the results of various kinetic methods based on DSC. Some authors (Borchardt and Daniels, 1957; Freeman and Carrol, 1958; Carroll and Manche, 1972) preferred the heat evolution method, which is based on the shape of a single DSC curve, whereas others (Duswalt, 1974; Ozawa, 1975) found an approach using a series of DSC experiments at various heating rates to be much more satisfactory.

In the present work, glassy felodipine was prepared by cooling the melt and the glassy state was confirmed by the X-ray diffraction method, scanning electron microscopy (SEM) and differential scanning calorimetry (DSC). The glassy felodipine was prepared at different cooling rates of the melt and the glass transition temperature, T_g, jump of the heat capacity, Δc_p, anomalous endothermic peak (relaxation enthalpy), ΔH_{relax}, crystallization kinetic constants and melting enthalpies were determined by the DSC experiments at various heating rates.

The dissolution rate of different types of glassy felodipine was also studied in the present investigation. Felodipine is a slightly water-soluble drug. Thus the dissolution rate could be the rate limiting process in the absorption of felodipine from a solid dosage form. Since the therapeutic dose of the drug is relatively large (10 mg), the poor aqueous solubility would result in dissolution and bioavailability problems on peroral dosing. Numerous attempts were conducted so as to develop an increased dissolution rate.

Experimental

Materials

Felodipine, a vasodilatory substance, is chemically a dihydropyridine derivative (Fig. 1). Crystalline felodipine with a melting point of 143°C (Kofler method) was used. The average diameter of crystalline felodipine particles was 10 μm.

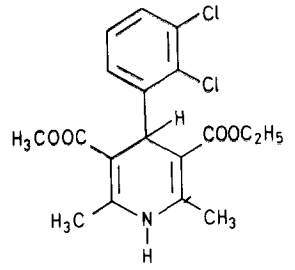

Fig. 1. Chemical structure of felodipine.

Preparation of glassy felodipine

For DSC studies, the crystalline felodipine was melted in an aluminium sample pan above melting temperature and the melts were solidified by cooling to 293 K at various rates. For dissolution studies, SEM and X-ray diffraction studies, the crystalline felodipine was melted in a glass pot and the melt was solidified either by cooling slowly at room temperature or by quenching in liquid nitrogen, thereafter being dried in a vacuum drier.

X-ray diffraction studies (Guinier powder method)

An Enraf Nonius instrument (Evershed-Enraf, Delft, The Netherlands) equipped with X-ray film as a detector was used for these studies. Powdered samples of a mixed size range were mounted on adhesive tape and the X-ray diffraction patterns were determined using CuK_α radiation.

Every experiment was carried out under following conditions: target, Cu; voltage, 36 kV; current, 16 mA; exposure time, 1.5 h. Evaluation of X-ray films was carried out using transmission densimetry.

Scanning electron microscopy

The shape and the surface appearance of crystalline and glassy felodipine were observed with a scanning electron microscope (SEM, JSM-U2; JEOL, Tokyo, Japan). The samples were prepared by shadowing with carbon and gold/palladium and observed with the secundar electron technique.

Thermal analysis

A Perkin Elmer DSC-4 (Perkin-Elmer, Norwalk, CT, U.S.A.) was used. All thermal analysis measurements were performed in a dynamic nitrogen atmosphere (40 ml/min). The sample sizes were in the range of 2–4 mg. The glass transition was observed as a discontinuity due to an increase in heat capacity of felodipine on the ordinate of the DSC curve, as shown in Fig. 2. The T_g is evident as a small endothermic rise, represented by the midpoint of the rise measured from the extension of the pre- and post-transition baselines, i.e. when the transition assumes half the value of this change.

The area under the anomalous endothermic peak is determined by extrapolating the post-transition baseline. The absorbed or evolved energy of the samples was calculated by measuring the peak area with a Perkin-Elmer Thermal Analysis Data Station 3700.

The Arrhenius pre-exponential factor, A, activation energy, E_a, and the order of crystallization, n, of the glassy felodipine were calculated through temperature-programmed DSC experiments according to a published method (Torfs et al., 1984).

The activation energy of crystallization was also calculated according to a previous method which examines exothermic peak maximum temperatures at different heating rates (Ozawa, 1975).

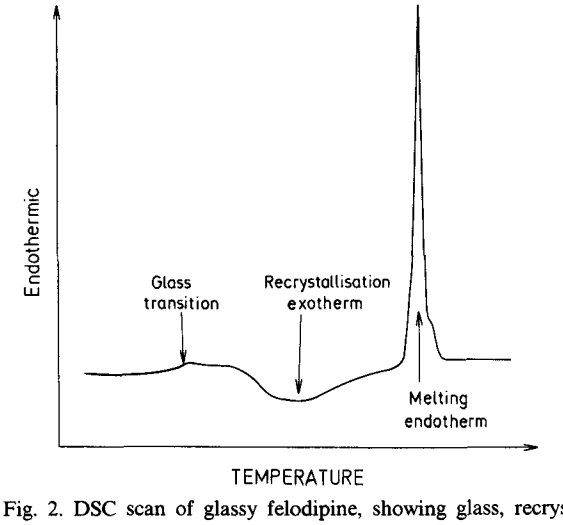

Fig. 2. DSC scan of glassy felodipine, showing glass, recrystallization and melting transitions; scan rate: 40 K/min.

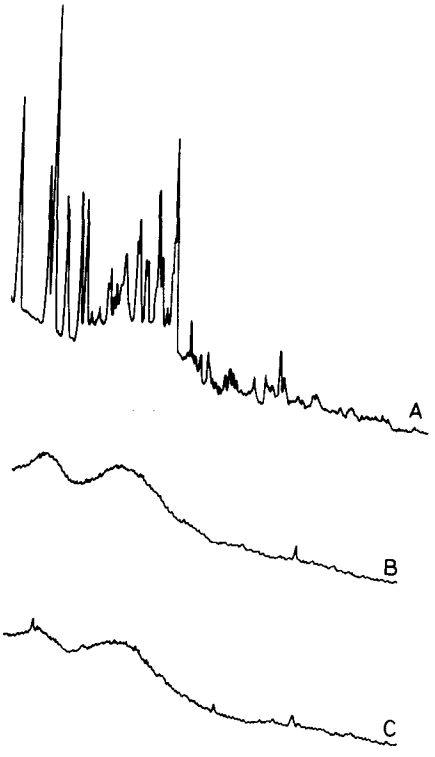

Fig. 3. X-ray diffraction patterns of crystalline and glassy felodipine. (A) Crystalline felodipine; (B) glassy felodipine prepared by cooling at room conditions; (C) glassy felodipine prepared by quenching in liquid nitrogen.

Dissolution studies

The dissolution studies were conducted in distilled water-ethanol (7 : 3, v/v) medium. The drug stability was satisfactory in this dissolution media after 2 h of exposure at 37 °C.

The USP Paddle method (USP XXI, 1985) was used to determine the dissolution rate of the samples: 1000 ml of dissolution medium, 37 °C, 100 rpm.

Accurately weighted drug samples (10 mg) were spread over the dissolution medium surface. Aliquots of the dissolution medium were withdrawn periodically and passed through a 0.45 μm membrane filter. The absorbance was determined spectrophotometrically at $\lambda = 346$ nm using Hewlett-Packard 8451A spectrophotometer.

Immediately after withdrawing an aliquot, an equal quantity of dissolution medium was added to maintain a constant volume. Cumulative cor-

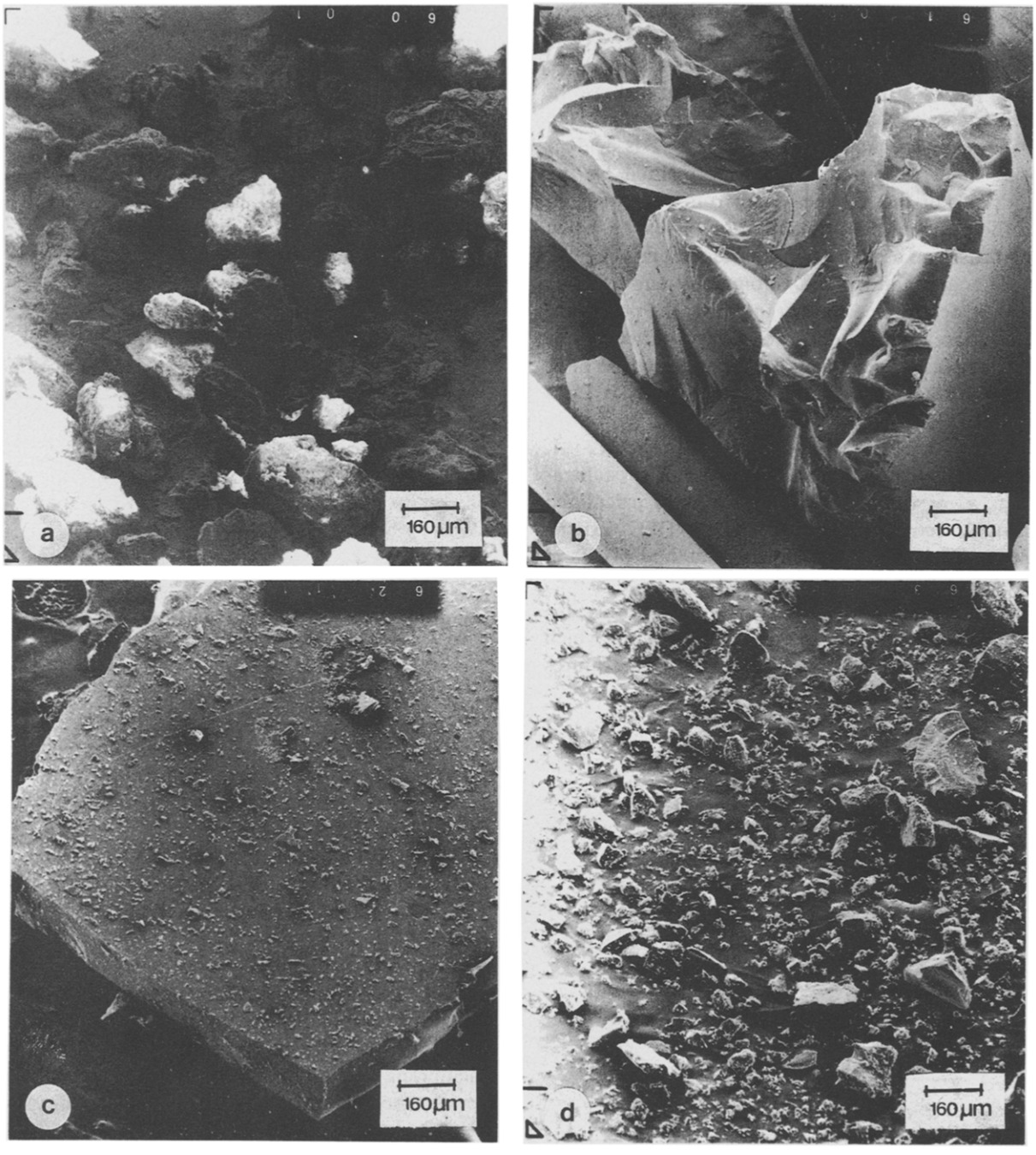

Fig. 4. Scanning electron micrographs of felodipine: (a) crystalline felodipine; (b) glassy felodipine, prepared by quenching in liquid nitrogen; (c) glassy felodipine, prepared by cooling under room conditions; (d) glassy felodipine, prepared by cooling under room conditions and pulverised in mortar.

rections were made for the previously withdrawn aliquots in calculating the total amount of felodipine dissolved.

Results and Discussion

Confirmation of the amorphous state of solidified melt by X-ray diffraction method and scanning electron microscopy

Fig. 3 shows X-ray diffraction patterns of the crystalline felodipine and felodipine, immediately after solidification of the melt at room conditions or in liquid nitrogen. In the case of solidified melt, no characteristic peaks were observed on the X-ray diffraction patterns: the solidified melt was in amorphous state.

Scanning electron micrographs of the crystalline and glassy felodipine particles are shown in Fig. 4. Irrespective of the method of solidification (slow or fast cooling), the solidified melt was a transparent and brittle glassy mass.

Thermal analysis

Influence of the cooling rate during glass preparation on the glass transition. It is generally accepted that glass formation depends on the cooling rate of the melt. To examine the effect of the cooling rate on the glass formation, glassy felodipine was prepared at various cooling rates and the glasses thus obtained were reheated with the rate of 10 K/min. In DSC thermograms, the jump of the heat capacity and the anomalous endothermic peak (heat capacity maximum) was observed under all conditions employed and it was suggested that a glass was formed irrespective of the cooling rate. The magnitude of the jump of heat capacity was almost the same in all cases (see Table 1). T_g varied at various cooling rates only from 317.5 to 318.5 K. The anomalous endothermic peak varied from 0.43 cal/g in the case of a cooling rate of -1 K/min to 0.11 cal/g for a cooling rate of -320 K/min (Table 1). Thus, the anomalous endothermic peak increased with decreasing cooling rate of the melt. The endothermic peak that accompanied the jump of the heat capacity was connected with the dynamics of freezing of molecular movement. The energy of the anomalous endothermic phenomenon was reported to reflect the quantity of relaxation of the glass.

Influence of the heating rate on glass transition. The melts were cooled at room conditions to 293 K and reheated at various heating rates. The DSC results are shown in Fig. 5; the jump of heat capacity and the anomalous endothermic peak can be seen in all cases. The glass showed different DSC curves due to the structural relaxation process during continuous heating at different heating rates. Thus, to prevent the glass from recovering enthalpy of relaxation during heating, a fast heating rate was desirable. Studies of the effect of the heating rate on T_g revealed that T_g increased as the heating rate was increased (see Table 2). A linear relationship was observed when the logarithm of the heating rate was plotted vs $1/T_g$. The apparent activation energy of the glass transition

TABLE 1

Influence of different cooling rates of the melt on felodipine glass transition

Cooling rate (K/min)	T_f (°C)	T_{mid} (T_g) (°C)	T_m (°C)	Δc_p (cal/g per degree)	Anomalous peak (cal/g)
−1.0	45.60	45.37	50.82	0.1006	0.43
−2.5	45.00	45.02	50.35	0.0829	0.32
−5.0	43.46	44.31	49.67	0.1061	0.26
−20.0	44.02	44.79	49.60	0.0966	0.18
−50.0	43.28	44.92	49.93	0.1102	0.12
−150.0	44.19	45.22	49.67	0.0840	0.11
−320.0	43.89	45.16	49.41	0.0983	0.11

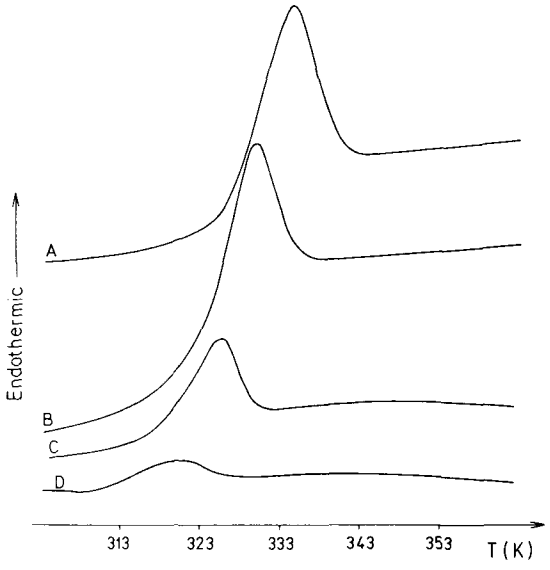

Fig. 5. Variation of T_g with heating rate of glassy felodipine. Heating rate: (A) 80.0; (B) 40.0, (C) 20.0; (D) 10.0 K/min.

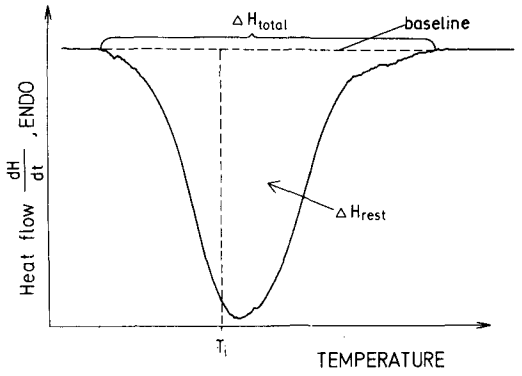

Fig. 6. DSC curve for glassy felodipine crystallization; the area between the curve and the broken baseline represents the heat of reaction, ΔH_{tot}, and the fraction of felodipine, which has not yet crystallized at temperature T_i, is related to ΔH_{rest}.

was calculated to be 31.6 kcal/mol according to Eqn 1 derived by Barton (1969).

$$\log \phi = \frac{E_a}{RT_g} \tag{1}$$

Influence of the heating rate on glassy felodipine crystallization. Heat evolution method: If samples are not too large (below 20 mg), the heat flow signal is as a good approximation directly proportional to the instantaneously evolved heat. Accordingly, the instantaneous reaction rate can be derived from the measured heat flow. Under these conditions the reaction rate constant, k, at any temperature, T_i, may be calculated from Eqn 2 (Carroll and Manche, 1972; Torfs et al., 1984).

$$k = \frac{dH}{dt} \cdot \frac{1}{\Delta H_{tot}\left(\frac{\Delta H_{rest}}{\Delta H_{tot}}\right)^n} \tag{2}$$

In Eqn 2, dH/dt is the heat flow (more exactly the flow deviation from the base line), ΔH_{tot} is the total heat of reaction evolved, which can be derived from the integral area of the reaction exotherm in Fig. 6, ΔH_{rest} is the reaction heat evolved above the temperature T_i (Fig. 6), and n is the order of the reaction. The reaction rate constant, k, is computed using Eqn 2 for $n = 0$, 1, 2 and 3. This yields a number of Arrhenius plots of which the one corresponding to the true reaction order should be linear. Fig. 7 is an example of such a plot of ln k vs reciprocal temperature for

TABLE 2

Influence of the heating rate on felodipine glass transition (sample: glassy felodipine, prepared by cooling the melt under room conditions)

Heating rate (K/min)	T_f (°C)	T_{mid} (T_g) (°C)	T_m (°C)	Δc_p (cal/g per degree)	Anomalous peak (cal/g)
10.0	40.40	40.49	48.24	0.0893	0.26
20.0	44.40	44.41	52.53	0.0760	0.82
40.0	49.28	50.38	56.71	0.0840	0.42
80.0	52.26	53.12	61.35	0.0934	1.26

the crystallization of the pulverised glassy felodipine, prepared by cooling the melt at room temperature and reheated at a heating rate of 10 K/min. The most perfect linear curve is selected. However, since none of the Arrhenius plots is really straight, the selection of the best linear curve can be complicated in some instances.

In many cases, however, the order of the reaction is known from other sources. Most crystallizations follow a first-order mechanism. As the order of the glassy felodipine crystallization was assessed, the kinetic crystallization parameters, i.e. the preexponential factor, A, and the activation energy, E_a, which are related to the rate constant, k, by the Arrhenius equation

$$k = A \exp(-E_a/RT)$$

were derived from this plot.

The glassy felodipine, prepared by cooling the melt at room temperature and thereafter pulverised, was characterised with this method. Using the heat evolution method, the calculated activation energy differed from 20.8 kcal/mol at a heating rate of 80 K/min to 35.2 kcal/mol at a heating rate of 10 K/min. The kinetic parameters obtained with this heat evolution method are dependent on the heating rate used in the DSC as shown in Table 3.

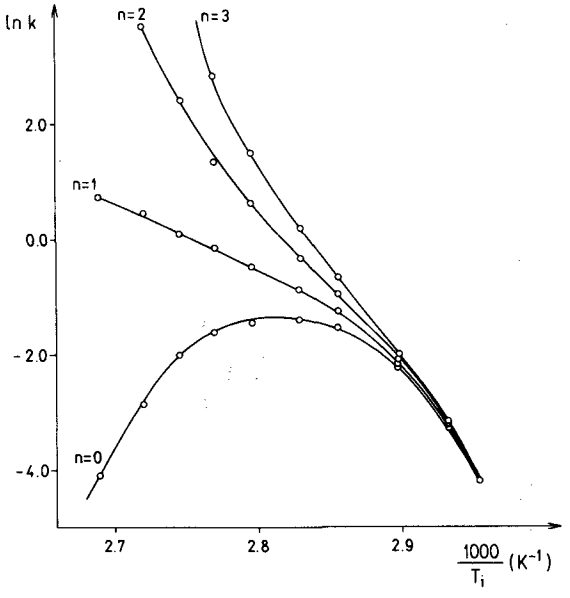

Fig. 7. Arrhenius plot for pulverised glassy felodipine crystallization, calculated from DSC data according to Eqn 2, for various reaction orders.

TABLE 3

Influence of the heating rate on crystallization kinetic constants, using heat evolution method (sample: pulverised glassy felodipine, prepared by cooling the melt under room conditions)

Heating rate (K/min)	Activation energy E_a (kcal/mol)	Preexponential factor ln A (1/min)
10.0	35.22	48.81
20.0	26.64	36.39
40.0	20.42	27.35
80.0	21.00	28.41

TABLE 4

Influence of the heating rate on glassy felodipine crystallization, variable heating rate method (sample: pulverised glassy felodipine, prepared by cooling the melt under room conditions)

Heating rate (K/min)	Onset T (°C)	T_m (°C)
10.0	67.71	80.17
20.0	71.70	87.10
40.0	77.18	97.96
80.0	83.72	104.60

Variable heating rate method: This DSC method, based on the work of Ozawa (1975), measures exothermic peak maximum temperature variations depending on changes in linear programmed DSC heating rates. Table 4 presents the peak temperatures obtained at various heating rates for glassy felodipine, solidified at room temperature and thereafter pulverised in the mortar. The plot of ln(heating rate) as a function of the reciprocal peak maximum temperature was found to be in line with anticipated linearity in the range from 10 to 80 K/min. The activation energy of 21.7 kcal/mol was obtained from an Arrhenius plot.

Influence of preparation method on felodipine melting. Crystalline felodipine melting was noted in the DSC curve as a sharp symmetrical endothermic peak with melting enthalpy of 20.85 cal/g. In contrast, asymmetrical melting peaks were observed in DSC curves in the case of recrystallized

glassy felodipine. Melting enthalpies for recrystallized glassy felodipine, prepared by solidification at room conditions or in liquid nitrogen were established to be 9.34 or 15.18 cal/g, respectively.

Dissolution studies

It is recommended that the dissolution rate can be determined under so-called 'sink conditions'; this term has been interpreted to mean that the concentration of the drug in the dissolution fluid must not exceed 10–20% of the saturation concentration (Moller, 1981). The use of dissolution tests has been questioned in the case of lipophilic drugs of extremely low water solubility. Felodipine is practically insoluble in water, the solubility at 37 °C being about 1 mg/l. Difficulties associated with the dissolution testing of lipophilic drugs became evident during the formulation process of a tablet that contained 10 mg felodipine. A method based on pure water as a dissolution medium would have required about 30 l of medium to ensure sink conditions. The handling of such a large volume is by no means practical.

The dissolution tests were performed in 30% ethanol in which the solubility of felodipine is about 4 g/l, being more than enough to maintain sink conditions. The felodipine concentration in samples was calculated as percent dissolved vs time t. Fig. 8 shows dissolution profiles of the crystalline and glassy felodipine: glassy felodipine, prepared by cooling the melt in liquid nitrogen or under room conditions has larger dissolution rates (0.072 or 0.042 1/min, respectively) than crystalline felodipine (0.019 1/min). An increase of felodipine dissolution rate may influence its absorption characteristics after peroral administration.

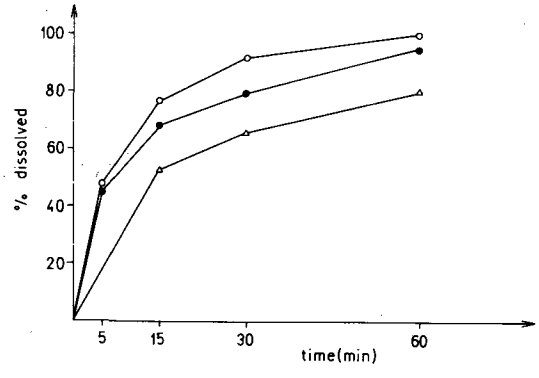

Fig. 8. Dissolution of felodipine by paddle method in water-ethanol medium. (△) Crystalline felodipine; (●) glassy felodipine, prepared by cooling under room conditions; (○) glassy felodipine, prepared by quenching in liquid nitrogen.

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