International Journal of Pharmaceutics, 87 (1992) 1–10

IJP 02806

Research Papers

Investigation of felodipine polymorphism and its glassy state

S. Srčič [a], J. Kerč [b], U. Urleb [a], I. Zupančič [c], G. Lahajnar [c], B. Kofler [b] and J. Šmid-Korbar [a]

[a] *Department of Pharmacy, University of Ljubljana, Aškerčeva 9, 61000 Ljubljana (Slovenia),* [b] *Department of Research and Development, Lek, Pharmaceutical and Chemical Works, Ljubljana (Slovenia) and* [c] *Institute Jožef Stefan, Ljubljana (Slovenia)*

(Received 27 March 1991)
(Modified version received 8 November 1991)
(Accepted 30 January 1992)

Key words: Felodipine; Polymorphism; Glassy state; DSC; X-ray diffraction; NMR; Spin-lattice relaxation time; Spin-spin relaxation time; Fourier transform infrared spectroscopy; Scanning electron microscopy

Summary

Felodipine (ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate) was investigated by means of DSC, FTIR and X-ray diffraction and three different polymorphic forms, designated as I–III, respectively, were found. During heating, no interconversion of any polymorphic form took place. After cooling the felodipine melt (in liquid N_2 or at ambient temperature) the glassy state was formed. The existence of glassy felodipine was confirmed by spin-lattice (T_1) and spin-spin (T_2) relaxation time measurements on a Bruker Pulse NMR spectrometer. During the heating of glassy felodipine recrystallization took place and two additional polymorphic forms, referred to as Im and IIIm, were observed.

Introduction

Felodipine (ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate) (Fig. 1), a Ca^{2+} antagonist, is a member of the dihydropyridine family where analogs such as nifedipine, nitrendipine and nicardipine are found. It is a very sparingly water-soluble drug. Its aqueous solubility has been determined to be 0.5 mg/l at ambient temperature (Anderberg et al., 1988) and reports on the solubility and dissolution rate enhancement have recently appeared (Schmidt et al., 1986; Anderberg et al., 1988).

The glassy state of felodipine has been prepared and analyzed, improvement in the dissolution rate of glassy felodipine also being confirmed (Kerč et al., 1991).

However, the polymorphism of felodipine, according to the latest literature, has not been investigated and therefore remains to be reported (Borka and Haleblian, 1990).

Different polymorphic forms of the felodipine analogs, nifedipine (Eckert and Müller, 1977) and nitrendipine (Kuhnert-Brandstätter and Völlenklee, 1986) have been reported. Consequently, felodipine was also predicted to exist in various polymorphic forms, due at least to the conforma-

Correspondence to: S. Srčič, Dept of Pharmacy, Faculty of Natural Sciences and Technology, University of Ljubljana, Aškerčeva 9, 61000 Ljubljana, Slovenia.

tion of the phenyl ring at position H(4) (Berntsson and Carter, 1981).

Experimental

Materials

Laboratory felodipine samples A (Resfar, Italy), B (Luwitrade, Liechtenstein) and C (Lek, Slovenia) were used as received. The average diameter of felodipine particles was about 10 μm.

Preparation of glassy felodipine

The felodipine powder was melted in a glass pot and the melt was solidified by quenching in liquid nitrogen or at ambient temperature and thereafter dried in a vacuum drier. Samples prepared in this way were used for DSC analysis. In the case of NMR studies the felodipine melt was cooled spontaneously in the NMR tube under ambient conditions.

Thermal analysis

A Perkin Elmer DSC-4 (Perkin-Elmer, U.S.A.) instrument was used. The thermal behavior of polymorphic forms was studied in a dynamic nitrogen atmosphere (40 ml/min) at a heating rate of 10 K/min. Sample sizes were in the range of 2–4 mg and were sealed in an aluminum pan. An empty sealed aluminum pan was used as a reference. Evaluation of the results was based on the special software of Perkin-Elmer together with a Data Station 3700.

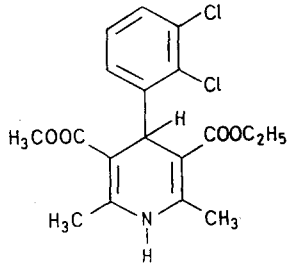

Fig. 1. Chemical structure of felodipine (ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate.

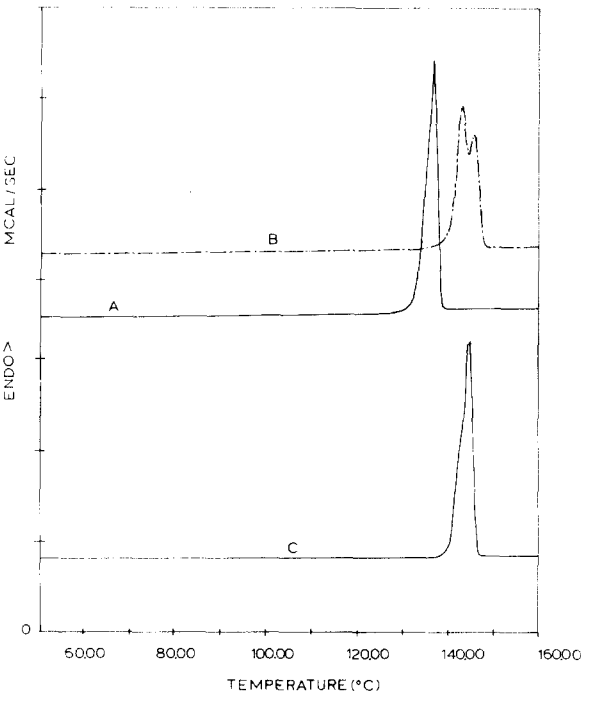

Fig. 2. DSC thermograms of felodipine samples A.

FT IR spectroscopy

The infrared spectra in KBr pellets were recorded over the wavenumber range of 4500–450 cm^{-1} with a Perkin-Elmer FT IR 1600 spectrometer (Perkin-Elmer, U.S.A.).

Scanning electron microscopy

The shape and appearance of the surface of felodipine forms A–C were observed using a scanning electron microscope (SEM, DSM-U2, Jeol, Japan). The samples were prepared by shadowing with carbon and gold/palladium and observed by using the secundar electron technique.

X-ray diffraction

An Enraf Nonius instrument (Evershed-Enraf, Delft, The Netherlands) equipped with X-ray film as a detector was applied 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 radiation.

Each experiment was carried out under the 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.

Pulse NMR

Crystalline felodipine (sample B) was heated stepwise in the NMR glass tube to a temperature exceeding the melting point (approx. 160°C). During the process of heating, the spin-lattice (T_1) and spin-spin (T_2) relaxation times at $\nu_H = 58.5$ MHz were measured on a Bruker pulse nuclear spectrometer B-KR 3228 (4–60 MHz). After heating and measuring the relaxation times T_1 and T_2 for crystalline felodipine, the NMR tube together with the melted sample was cooled spontaneously to ambient temperature. Glassy felodipine was formed. The measuring procedure described above was also carried out with glassy felodipine.

Results and Discussion

There is a lack of published data concerning the conditions for crystallization (e.g., solvents and temperatures) of samples A–C. For felodipine crystallized from 2-propanol solution (T_m = 142–143°C), the conformation of the phenyl ring in which the 2-chloro atom is close to H(4) was determined by ^{1}H-NMR spin-lattice relaxation time measurements (Berntsson and Carter, 1981). It appears that these conformational options on the H(4) position could essentially contribute to the conformational polymorphism of felodipine.

TABLE 1

Onset melting temperatures and melting enthalpies of the felodipine samples

Form	Felodipine sample		
	A	B	C
I	133.9°C 18.7 cal/g		
II		141.4°C	141.7°C 21.9 cal/g
III		144.9°C	

TABLE 2

Typical IR wavenumbers (cm^{-1}) of felodipine A–C

	Felodipine		
	A	B	C
NH	3333.6	3370.70	
CH aromatic	3104.3	3069.0	
CH aliphatic	2978.9	2979.3	
C=O ester	1697.9		
		1698.1	
	1682.1		
C=C	1618.2	1621.0	
C–CH_3	1382.3	1381.0	

Fig. 2 shows DSC thermograms of the investigated felodipine samples and Table 1 lists the onset melting temperatures and melting enthalpies of pure polymorphs. From these results three different felodipine polymorphs can be described. Since no literature data are available, they were designated as I (T_m = 133.9°C), II (T_m = 141.5°C) and III (T_m = 144.9°C). Samples A and C are pure polymorphs I and II, respectively, and B the mixture of II and III. Felodipine crystallized from 2-propanol is designated as polymorphic form II.

The slightly asymmetric melting peak of sample C may indicate the presence of a polymorphic mixture, however, it was not possible to separate them and therefore it was assumed to be a homogeneous polymorphic form.

As heating beyond the melting range of felodipine caused interconversion, the polymorphs found can be referred to as monotropic.

The infrared spectra of felodipine samples are depicted in Fig. 3 and the wavenumbers are listed in Table 2. A detailed IR study of felodipine is

TABLE 3

Glassy state parameters of felodipine samples A and C

Felodipine sample	T_g (°C)	ΔC_p (cal/g per degree C)	ΔH_r (cal/g)
A	42.7	0.076	0.24
C	43.7	0.068	0.22

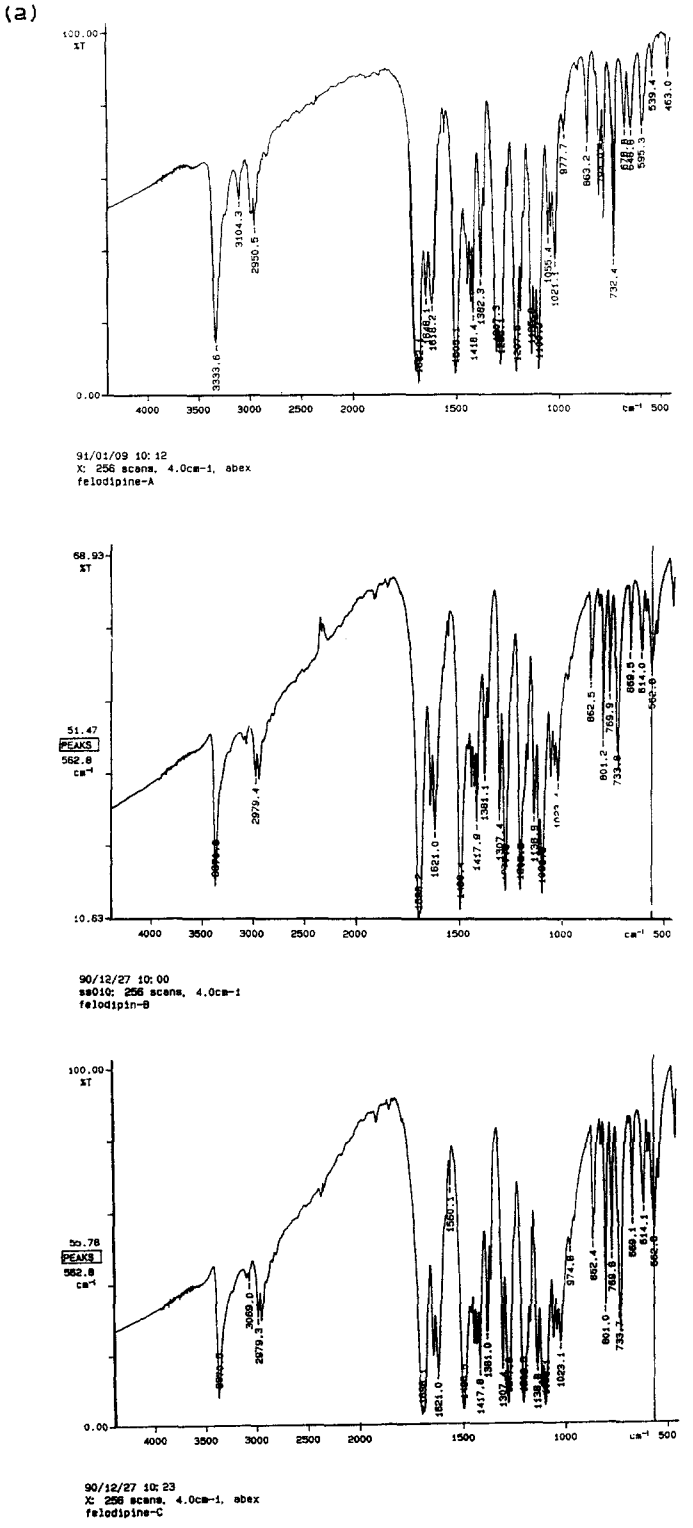

Fig. 3. (a) FT IR spectra of felodipine A–C. (b) Detailed FTIR spectra of samples A(X), B(Y), C(Z).

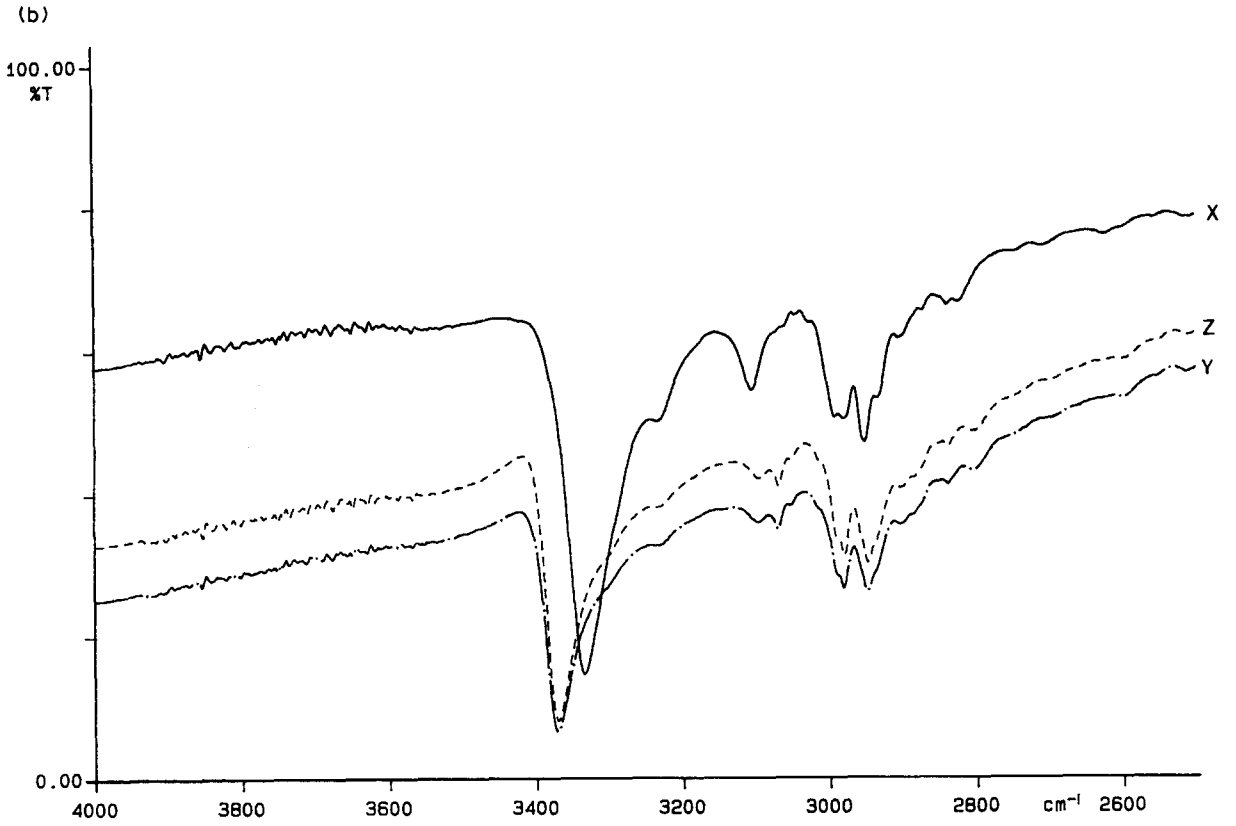

Fig. 3b.

currently underway (Srčič et al., in preparation). The presented results may lead to the conclusion that felodipine exists in at least two polymorphic forms. Felodipine A represents one form while samples B and C correspond to the other. The results actually correlate well with the data from thermal analysis, i.e., felodipine A is form I whilst B and C exist in form II. Sample B also includes form III, however, it was not found in the IR spectra. The greatest differences between the forms found by IR exist in the NH and -C-H aromatic stretchings. These results are in support of the previously published information about the possible conformations in the felodipine molecule which can play an important role in the polymorphism of felodipine.

The X-ray powder diffraction results shown in Fig. 4 demonstrate three different patterns, also in accordance with the above-mentioned DSC data.

The microscopic appearance of these samples is illustrated in Fig. 5. The differences are clearly visible. Some similarities between samples B and C could be found, thus supporting the obtained DSC results.

Felodipine polymorphic forms obtained from cooled melts

The behavior of felodipine from supercooled melts has been reported (Kerč et al., 1991). The glassy felodipine was found to be formed by cooling the melts in liquid nitrogen or at ambient temperature. The characteristics of the glassy state, i.e., T_g, ΔC_p and ΔH_r were detected, and no evident differences between samples A–C were found (Fig. 6 and Table 3).

These results were expected in view of the glassy state disorder. By heating the glassy felodipine (prepared at ambient temperature)

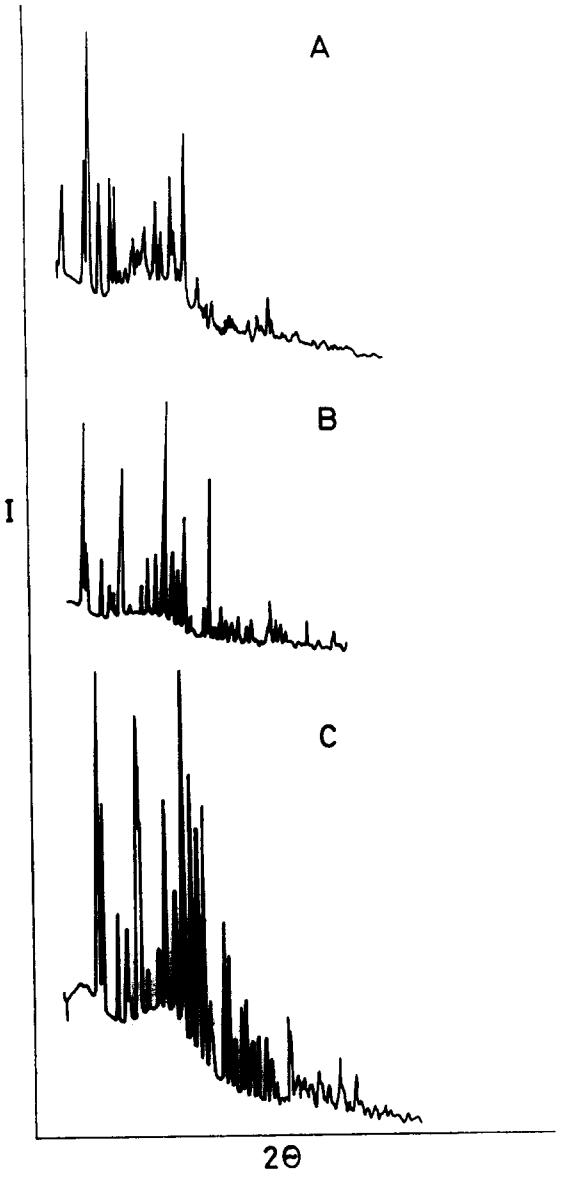

Fig. 4. X-ray powder diffraction patterns of felodipine A–C (x-axis, 2θ; y-axis, intensity).

above the T_g, first crystallization and thereafter melting of the formed crystals took place (Fig. 6). On comparing the melting temperatures of the original and recrystallized felodipines (Table 4), the existence of two additional polymorphic forms was confirmed (Im and IIIm). Form II (T_m = 140.5–141.5°C) was found in the original and recrystallized felodipine samples. Thermograms of glassy felodipine (sample A) prepared at liquid N_2 and at ambient temperatures are shown in Fig. 7, and the melting temperatures of forms detected are listed in Table 5.

Irrespective of the preparation method, glassy felodipine recrystallized into three polymorphic forms, Im, II and IIIm, respectively (see also Table 4). It is worth mentioning that no evidence of the original form I (T_m = 133.9°C) was obtained. The difference in onset temperature of recrystallization between the glassy forms prepared at ambient and liquid N_2 temperatures is evident, namely, about 10°C. From the previous results (Kerč et al., 1990), it appears that this temperature is related to the so-called relaxation enthalpy (ΔH_r) associated with the glass transition temperature. This endothermic relaxation process increased in extent with decreasing cooling rate of the felodipine melt. The differences between the 'ambient' and 'liquid N_2' glassy felodipine forms were also confirmed by dissolution testing: the liquid N_2 glass showed better solubility and greater dissolution rate (Kerč et al., 1991).

In the next step, the glassy felodipine prepared at ambient temperature (sample A) was pulverized using a mortar and pestle, the thermograms of this pulverized sample being shown in Fig. 8 and detailed in Table 6. Important differences were noted: the onset temperature of recrystal-

TABLE 4

Onset melting temperatures of polymorphic forms found for original and recrystallized felodipine samples

	T_m (°C)				
Original felodipine (A–C)	133.9 (I)		140.5 (II)	144.9 (III)	
Recrystallized felodipine (A)		137.6 (Im)	141.5 (II)		147.1 (IIIm)

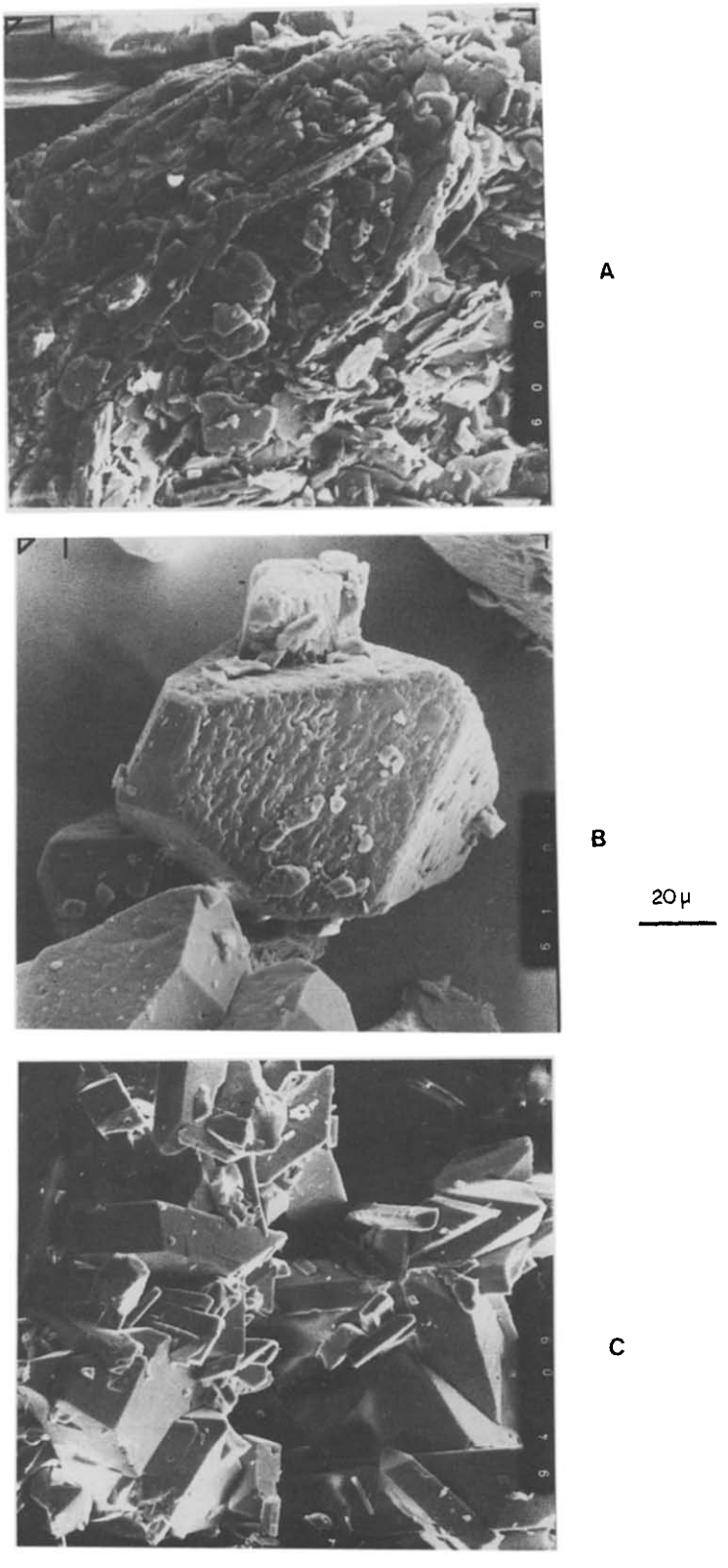

Fig. 5. Scanning electron micrographs of felodipine A–C.

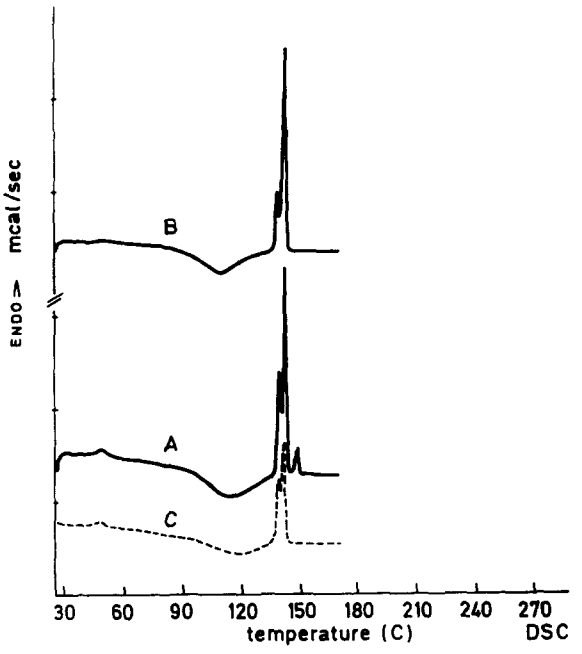

Fig. 6. DSC thermograms of glassy felodipine A–C. Glasses were prepared at ambient temperature.

lization was almost 30°C lower and only forms II and IIIm were found in the pulverized glass. It appears that the mechanical treatment contributes an additional amount of energy to the glassy state and thus that the onset temperature of recrystallization can be lowered. No evidence of form Im was found and only small quantities of form IIIm can be anticipated from the thermo-

TABLE 5

Onset melting temperatures of polymorphic forms of felodipine A and its recrystallized glasses

Felodipine sample	T_m (°C)				
Original (A)	133.9				
Recrystallized liquid N_2 glass		138.2	140.7	147.0	89.2 [a]
Recrystallized ambient glass		137.8	140.6	147.0	98.2 [a]

[a] Onset recrystallization temperatures of glasses.

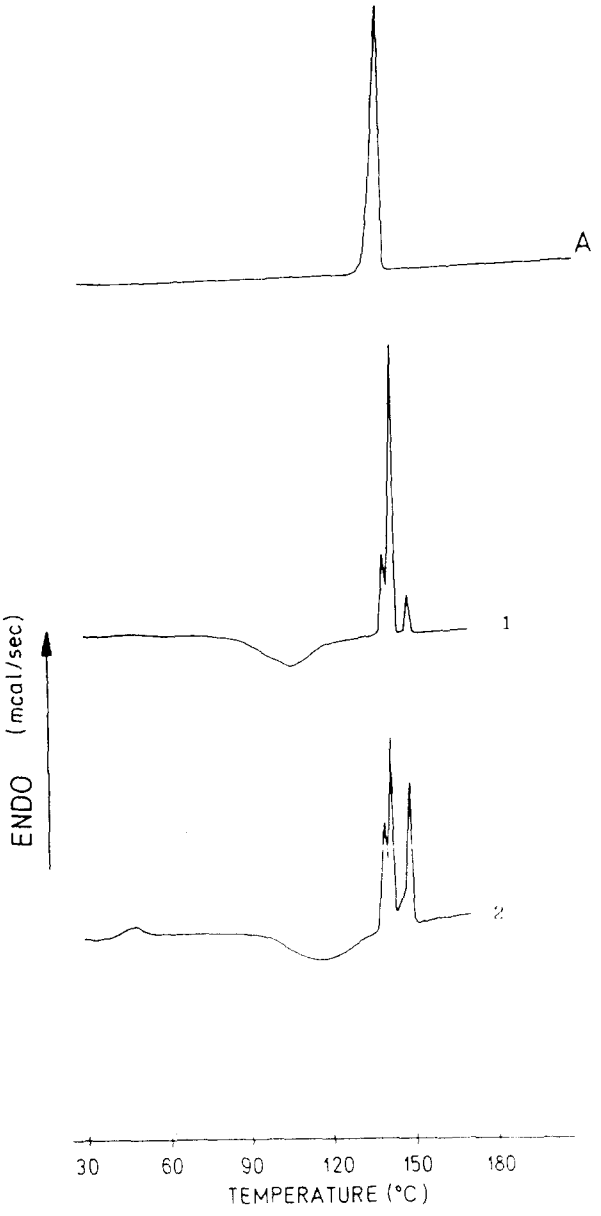

Fig. 7. DSC thermograms of felodipine A and corresponding glasses prepared at liquid nitrogen (1) and ambient (2) temperatures.

gram. The established results support the view that lower recrystallization temperature favors polymorphic form II, whilst higher temperature, i.e., that of the ambient glass, also leads to forms Im and IIIm.

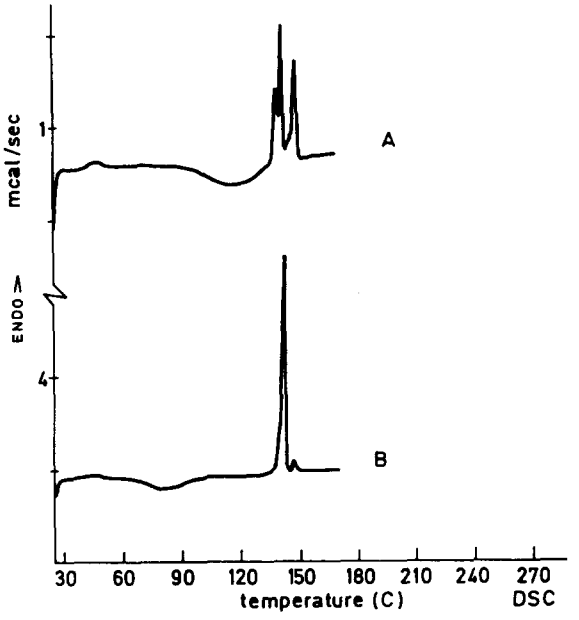

Fig. 8. DSC thermograms of glassy felodipine before (A) and after (B) pulverization (glassy felodipine prepared at ambient temperature).

Confirmation of the felodipine glassy state with NMR

The existence of glassy felodipine was confirmed by DSC, X-ray diffraction and SEM approaches (Kerč et al., 1991). The glassy felodipine was found to be transparent, brittle and unstable. The dissolution rate of the glass was proved to be greater compared to that of the crystalline form.

TABLE 6

Onset melting temperatures of felodipine forms before and after pulverization

Sample	T (°C)				
Felodipine (A)	133.9 (I)				
Recrystallized ambient glass		137.8 (Im)	140.6 (II)	147.0 (IIIm)	98.2 [a]
Recrystallized pulverized ambient glass			140.5	146.1	67.0 [a]

[a] Onset recrystallization temperatures of glasses.

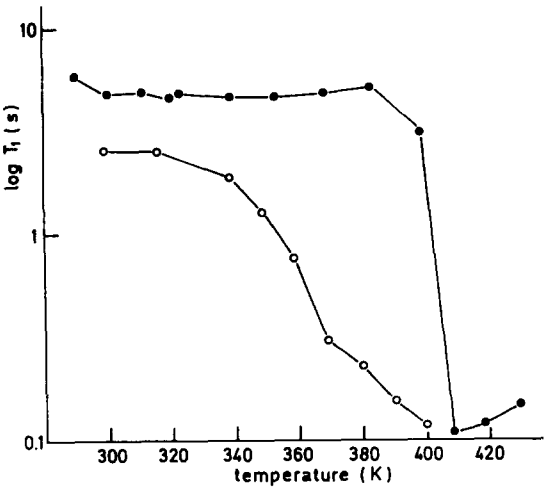

Fig. 9. Spin-lattice relaxation time (T_1) determined during heating of felodipine (●) (sample B) and its glassy state (○).

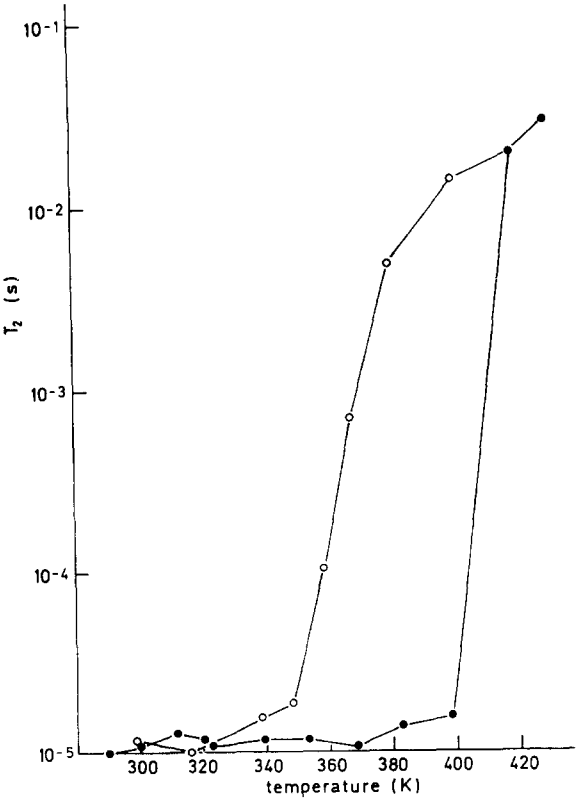

Fig. 10. Spin-spin relaxation time (T_2) evaluated during heating of felodipine (●) (sample B) and its glassy state (○).

A rather infrequently used method for confirmation of the material glassy state is pulse NMR spectroscopy. By observing the spin-lattice relaxation time (T_1) and spin-spin relaxation time (T_2), the glassy state can be indisputably confirmed. When heating the crystalline materials, the observed times T_1 and T_2 will be changed due to a jump in the melting temperature. In contrast, the relaxation times T_1 and T_2 will undergo gradual alteration in the case of the glass. Figs 9 and 10 demonstrate such behavior and therefore provide further confirmation of the above-described glassy state of felodipine.

Conclusion

The original felodipine samples exist in three different polymorphic forms, I–III, that are stable. After the recrystallization of the glassy state, two additional polymorphic forms, Im and IIIm, were observed. The gradual change in the spin-lattice and spin-spin relaxation times confirms the existence of the glassy state of felodipine described in the literature.

References

Anderberg, E.K., Bisrat, M. and Nyström, C., Physicochemical aspects of drug release. VIII: The effect of surfactant concentration and drug particle size on solubility and dissolution rate of felodipine, a sparingly soluble drug. *Int. J. Pharm.*, 47 (1988) 67–77.

Berntsson, P. and Carter, R.E., Determination of the conformation of felodipine by ^{1}H NMR spin-lattice relaxation time measurements. *Acta Pharm. Suec.*, 18 (1981) 221–226.

Borka, L. and Haleblian, J.K., Crystal polymorphism of pharmaceuticals. *Acta Pharm. Jugosl.*, 40 (1990) 71–94.

Eckert, T. and Müller, J., Über polymorphe Modifikationen des Nifedipine aus Unterkühlten Schmelzen. *Arch. Pharm.*, 310 (1977) 116–118.

Kerč, J., Srčič, S., Mohar, M. and Smid-Korbar, J., Some physico-chemical properties of glassy felodipine. *Int. J. Pharm.*, 68 (1991) 25–33.

Kuhnert-Brandstätter, M. and Völlenklee, R., Beitrag zur Polymorphie von Arzneistoffen. 2. Mitt.: Halofenat, Lorcainidhydrochlorid, Minoxidil, Mopidamol und Nitrendipin. *Sci. Pharm. (Wien)*, 54 (1986) 71–82.

Schmidt, W., Luchtenberg, H. and Porges, E., Feste Arneizubereitungen mit Dihydropyridinen und Verfahren zu Ihrer Herstellung. DE 3424553/A1.