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POLYMORPHISM AND STABILITY OF NORFLOXACIN, (1-ETHYL-6-FLUORO-1,4-DIHYDRO-4-OXO-7-(1-PIPERAZINIL)-3-QUINOLINOCARBOXYLIC ACID

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Norfloxacin was studied by thermal methods (TG and DSC), X-ray powder diffraction, and by FT-IR, UV-VIS and NMR spectroscopy. The drug substance can be prepared in two different crystalline forms and in amorphous state, depending on the experimental conditions of preparation. DSC examinations were carried out at various heating rates and by cycling the samples in the temperature range 50°–250°C. The unstable crystalline form undergoes two irreversible solid-solid phase transitions at 176.5° and 195.6°C. The polymorph melts in the temperature range 218.5°–220.0°C.

Keywords: drug, norfloxacin, polymorphism, stability

Introduction

Polymorphism is very common among pharmaceutical substances. As the polymorphs possess different internal organization within the solid, they often show different melting points, solubilities, chemical reactivity or stability. These can appreciably influence pharmaceutical properties such as dissolution rate and bioavailability. It is therefore important to evaluate the polymorphism in early stages of new formulation studies [1, 2].

Norfloxacin, a derivative of 4-quinolone carboxylic acid, has a wide spectrum of antimicrobial activity covering both gram-negative and gram-positive organisms [3]. There are no data on phase transitions for this substance in the literature except for the melting point at 227°–229°C [4]. In the present study, the polymorphism of norfloxacin, together with the ranges of stability of polymorphs has been examined.

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Table 1 X-ray powder patterns of FORM A and FORM B of norfloxacin

FORM A		FORM B	
d /Å	*I*	*d* /Å	*I*
15.90	1	11.37	2
9.05	44	11.09	3
8.32	3	9.60	6
7.76	6	8.99	5
7.23	16	8.46	3
5.98	8	8.30	6
5.55	58	8.07	4
5.30	3	7.80	6
4.76	10	7.17	2
4.50	14	6.73	11
4.33	55	6.63	15
4.15	17	6.35	3
3.95	48	5.78	2
3.86	12	5.63	6
3.77	14	5.50	20
3.65	38	5.33	23
3.60	100	5.19	12
3.64	27	4.70	100
3.47	20	4.61	30
3.40	17	4.49	4
3.35	11	4.31	24
3.25	20	4.25	15
3.09	9	4.17	9
3.07	10	4.08	20
		3.96	68
		3.82	7
		3.74	7
		3.69	9
		3.62	11
		3.57	16
		3.54	24
		3.46	10
		3.34	7
		3.30	5

Experimental

Norfloxacin synthesized in Krka, Pharmaceutical Industry (FORM A) and a commercial sample from CPB International INC (FORM B) were used. Amorphous norfloxacin was prepared by spray drying on a Mini Spray Dryer Buchi 190 and by quenching the melted samples. All the samples were chromatographically pure.

Differential scanning calorimetry was carried out by means of a Perkin Elmer DSC-7 calorimeter equipped with water cooling. Experimental conditions: aluminium crucibles of 30 μl volume with four holes, atmosphere of dry nitrogen with 40 ml/min flow rate, heating rates 0.5–100 deg·min^{-1}, temperature range 50°–250°C. The calorimeter was calibrated daily for each heating rate with indium of 99.99% purity. Thermogravimetric curves were measured by a Perkin Elmer TGA-7 analyzer in opened platinum crucibles of 50 μl volume in an atmosphere of dry nitrogen.

X-ray diffraction patterns were obtained from a Philips PW 1710 powder diffractometer with CuK$_{\alpha 1}$ radiation. FT-IR spectra were recorded on a Perkin Elmer 1720x spectrometer in KBr pellets. UV-VIS spectra were measured in 0.1*M* NaOH with a concentration of 5 μg/ml by a Perkin Elmer Lambda 5 spectrometer. ^{1}H-NMR spectra were recorded on a Varian EM-360 L instrument in trifluoroacetic acid.

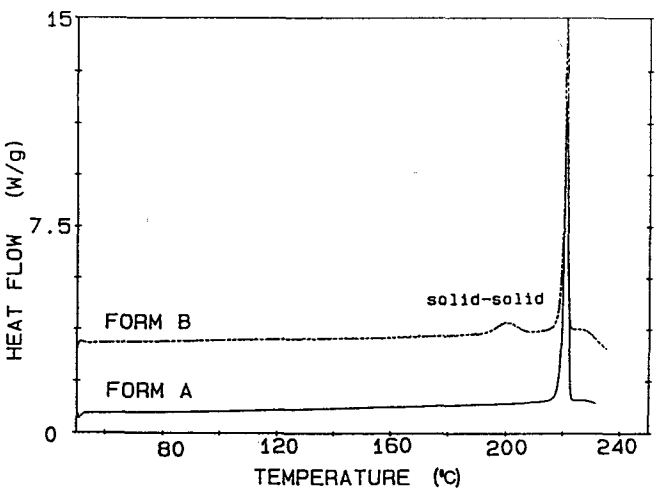

Fig. 1 DSC curves of two crystalline polymorphs (heating rate 10 deg·min^{-1})

Results and discussion

X-ray powder patterns for various samples of KRKA products (FORM A) are identical with the one reported by Yuasa [5]. FORM B exhibits an entirely different powder spectrum, proving the existence of two polymorphic modifications of norfloxacin (Table 1).

^{1}NMR and UV spectra of the two forms and of the amorphous substance mentioned later on proved the identity of the samples.

The DSC curve of FORM A (Fig. 1) shows a melting point only at 219.5°C. All the samples investigated melt in the range 218.5°–220.0°C. The DSC curve of FORM B has an additional endothermal effect at 195.6°C with no mass change in that temperature region, so it can be ascribed to solid-solid phase transition. The temperatures and the enthalpies of phase transitions are given in Table 2.

Table 2 Thermal data

	Melting		Transition	
FORM	T_m/°C	ΔH / J·g^{-1}	T_t/°C	ΔH_t / J·g^{-1}
A	219.5± 0.2	114.8± 1.2		
B	219.5± 0.2	115.2± 1.0	195.6± 0.2	20.0± 1.0

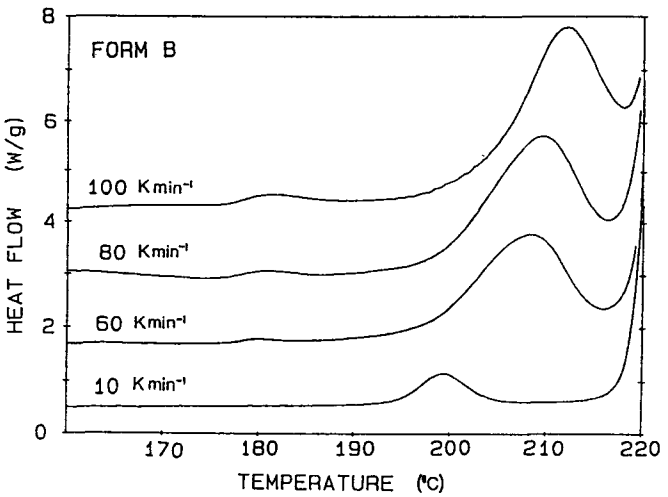

Fig. 2 DSC curves of FORM B as a function of heating rate

The influence of heating rate on the transition temperatures is represented in Fig. 2. The melting temperatures are independent of the heating rate, while the

temperature of the solid-solid phase transition at approximately 200°C, however, rises from 195.6° to 205.0°C with increasing heating rates. At higher heating rates the third transition at 176.5°C was identified. Its temperature also remains constant with the variation of heating rate. At low heating rates (0.5 deg·min^{-1}) neither of the two solid-solid transitions could be identified.

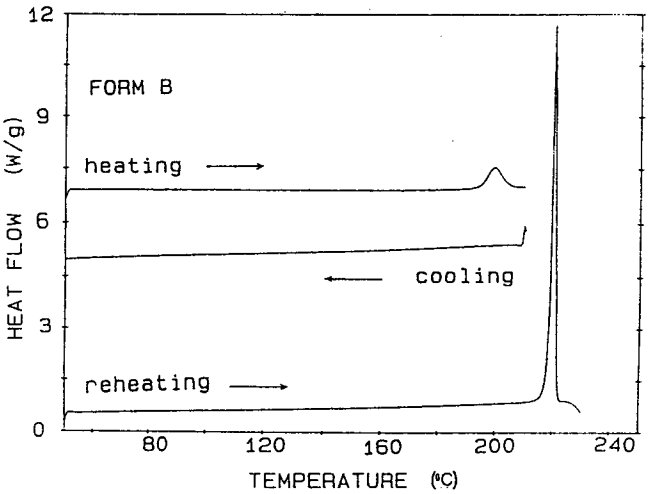

Fig. 3 DSC curves for heating and cooling (rate 10 deg·min^{-1})

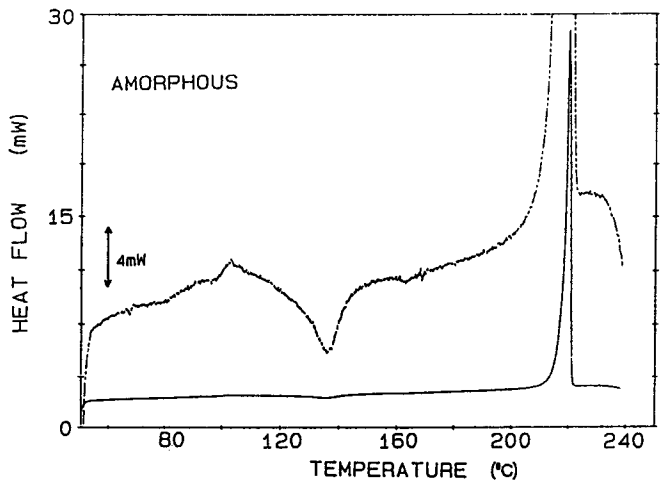

Fig. 4 DSC curves of amorphous sample (heating rate 10 deg·min^{-1})

To evaluate the nature of the phase change at 195.6°C the sample of FORM B was heated just above the transition temperature, cooled at the same rate and heated again to the melting point (Fig. 3). There is neither an exothermal effect on cooling nor an endothermal one on repeated heating proving that the transition at 195.6°C is monotropic.

The samples of FORM A were heated up to the melting point, quenched rapidly and heated again. In the second heating the exothermal effect appeared in the temperature range 105°–155°C due to the crystallization of partially amorphous norfloxacin. Apart from this weak exothermal peak, only the melting of samples was observed. The temperature of crystallization of the amorphous phase is lower than the solid-solid phase transition at 195.6°C indicating again a monotropic transition with one stable phase. The DSC curve for the amorphous norfloxacin prepared by spray drying also shows crystallization and melting and, on repeated heating, only melting (Fig. 4).

FT-IR spectra of the two polymorphic and of the amorphous phase show characteristic differences in the whole spectral region. These spectra are specific enough to be used independently for characterising various forms of norfloxacin (Fig.5)

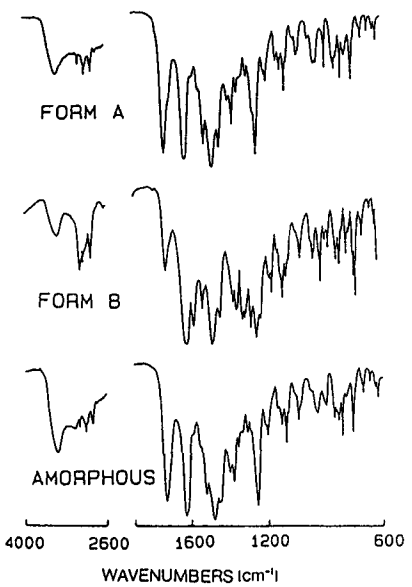

Fig. 5 FT-IR spectra of two crystalline polymorphs and of an amorphous sample

References

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Zusammenfassung — Norfloxacin wurde mittels thermischer Methoden (TG und DSC), weiterhin mittels der Debye-Scherrer-Methode und FTIR-, UV-VIS- und NMR-Spektroskopie untersucht. Je nach den experimentellen Bedingungen bei der Herstellung kann die Wirkstoffsubstanz in zwei verschiedenen kristallinen und in einer amorphen Form hergestellt werden. Die DSC-Untersuchungen wurden bei zahlreichen Aufheizgeschwindigkeiten und durch abwechselnden Temperaturwechsel zwischen Raum- und Schmelztemperatur durchgeführt. Die unstabile kristalline Form unterliegt zwei irreversiblen Feststoff-Feststoff-Umwandlungen bei 176.5° und bei 195.6°C. Das polymorphe Material schmilzt im Temperaturbereich 218.5°–220.0°C.