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Polymorphism in binary mixtures, as exemplified by nimodipine

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Abstract

The results of studies on nimodipine in the solid state demonstrate that the compound occurs in two polymorphic forms. Modification I melts at +124°C and crystallizes as the racemic compound. Modification II (m.p. +116°C) is a conglomerate. The two polymorphs have been characterized by means of differential scanning calorimetry, infrared, Raman, and ^{13}C-NMR spectroscopy, X-ray powder diffractometry, X-ray structure analysis, pycnometry, and solubility measurements. The thermodynamic relationships are illustrated in a semi-schematic energy/temperature diagram, which gives information about the relative stability and physical properties of the two modifications. Modification II is the stable form between absolute zero and about +90°C. The melting characteristics of the two polymorphs are illustrated by the phase diagram. Modification I is yellow. Modification II is almost white. The differences in colour are discussed with reference to the results of X-ray structure analyses and the UV-Vis spectra.

Keywords: Polymorphism; Nimodipine; Phase diagram; Conglomerate; X-ray structure; Drug; DSC; Thermodynamic stability

1. Introduction

Like inorganic compounds and elements, organic compounds can crystallize in more than one crystal form. The ability of a substance to exist in several different forms is known as polymorphism. The polymorphs of a compound are chemically identical, but they differ in respect of their physical properties, such as density, crystal habit, spectra, melting point, solubility, etc. (Burger, 1990).

Borderline cases of polymorphism occur in binary mixtures of the optical antipodes of a racemate. The definition of the term polymorphism can be restricted to differences in packing or arrangement of the same molecules in the crystal lattice (Burger, 1982). If a 50:50 mixture of the optical antipodes of a substance is a two-phase system it is called a conglomerate, if it is a single-phase system it is a racemic compound. According to this definition, racemic compound and conglomerate are not polymorphic forms of a substance.

Other authors regard conglomerate and racemic compound as modifications of a binary system (Jaques et al., 1981a; Brittain, 1990). Haleblian and McCrone (1969) base the definition on the physical properties in the different aggregate states: polymorphic forms exhibit dif-

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ferent physical properties when in the crystalline state and the same physical properties when in the liquid and gaseous state. A pragmatic view usually has to be taken in borderline cases of polymorphism (Burger, 1982). If a substance can crystallize as a racemic compound and as a conglomerate, each form easily transforms into the other, via the melt or in solution, with no chemical change. We therefore regard racemic compound and conglomerate as two modifications of one substance.

Polymorphism of drug substances has been the subject of intensive research for many years (Borka and Haleblian, 1990). The solubility of a drug substance in aqueous media may have a crucial bearing on its bioavailability. The modifications of a drug substance may also differ in respect of important pharmaceutical properties such as tabletting characteristics, stability of suspensions during storage, and millability. Therefore, knowledge of the physical properties and polymorphism of the drug substance is essential for the successful development of a new medicine.

Nimodipine [isopropyl(2-methoxyethyl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate] is a drug substance of the 1,4-dihydropyridine type which has been developed by Bayer AG (Meyer et al., 1983). Nimodipine has been licensed in Germany since 1984 for the prevention and treatment of ischaemic neurological deficits caused by spasm of cerebral vessels following subarachnoid haemorrhage.

Hitherto, to manufacture tablets, solutions of the drug substance have been used to produce coprecipitates in which nimodipine is present in the amorphous state. Thus far only the racemic compound has been used in the manufacture of drug products. However, it is not completely satisfactory for the manufacture of some drug products. For example, under storage conditions, crystal growth has been observed in suspensions for oral administration containing the racemic compound of nimodipine. As a result of this, sedimentation increases, leading to the formation of solid deposits on the bottom of the storage vessel, which considerably impair quality and dosing accuracy, and also the biological effects of this product.

Therefore, the development of new formulations in which nimodipine is present in the crystalline form (Grunenberg et al., 1992) needs the investigation of polymorphism in detail. In particular, more information is needed about thermodynamic stability, the different physical properties and the colour differences of the polymorphs (Burger and Lettenbichler, 1993). The methods used for these investigations are thermal analysis (Giron, 1990), vibrational spectroscopy (Grunenberg and Bougeard, 1986), NMR spectroscopy (Saindon et al., 1993), X-ray diffraction, and determinations of solubility and density.

2. Materials and methods

2.1. Materials

The studies on nimodipine were carried out using modifications I and II of the racemate and the pure optical antipodes from Bayer AG. The purity of nimodipine and the amino acids (Fluka) used as standard materials for density measurements was $> 99\%$. The solvents used were reagent grade commercial products (Merck, Riedel-de Haën). Standard materials used for thermal analysis were indium (99.9999%, Preussag) and alumel (Perkin-Elmer). Potassium bromide (Merck) was used for IR spectroscopy and polyethylene (Merck) for FIR spectroscopy.

2.2. Methods

DSC (differential scanning calorimetry) and TGA (thermogravimetry) investigations were carried out with a Perkin Elmer DSC 7/TGA 7 thermal analysis system. The accuracy of the temperature for the DSC analyses was ± 0.2 K; the error in the heat of fusion based on the indium standard was $\pm 2\%$. For the TGA analyses, the accuracy of the temperature was ± 2 K according to the alumel standard. The relative weight error of the thermobalance was $\pm 0.1\%$. The thermogravimetric measurements were carried out in an open platinum crucible. The DSC measurements were carried out in an aluminium capsule with a perforated lid.

The thermomicroscopic investigations were carried out with a Leitz Laborlux S thermomicroscope at a magnification of ×100 in linearly polarized light.

The NMR spectra were recorded, using a Bruker MSL 300 NMR spectrometer, at a measurement frequency of 75.47 MHz and a rotation frequency of 6460 MHz.

The UV-Vis spectrometer used was a Perkin Elmer Lambda 9. An Ulbricht sphere was used. The resolution was 1 nm; the cell paths were 10 and 2 mm.

Bruker Fourier IR spectrophotometers IFS 66 (IR), IFS 66v (FIR) and IFS 88 (Raman) were used for vibrational spectroscopy. The resolution of the IR and FIR spectra was 2 cm^{-1}; the resolution of the Raman spectra was 4 cm^{-1}.

The densities of the modifications were determined using a Quantachrome MPY-2 micropycnometer, with helium as the working gas. The measurement accuracy based on amino acids (glycine, DL-leucine) was ± 0.01 g cm^{-3}.

3. Results

3.1. Thermal analysis

The melting points and enthalpies of fusion of modifications I (racemic compound) and II (conglomerate) are shown in Table 1. The heat of fusion of modification II (46 kJ mol^{-1}) is significantly higher than that of modification I (39 kJ mol^{-1}). On the other hand, the melting points and enthalpies of fusion of the pure enantiomers are the same (m.p. 135°C, heat of fusion 47 kJ mol^{-1}), i.e. it was not possible to detect any difference with the method of measurement used.

The results of the thermomicroscopic investigations of molten films demonstrate that modification I crystallizes into coarse plates. If allowed to grow unimpeded, these plates are hexagonal. Modification II crystallizes from the melt in form of circular aggregates (rosettes). Thermomicroscopy and IR spectroscopy were used to identify the modification present in the films obtained by crystallization.

The thermomicroscopic contact method (Kofler et al., 1954) was used to construct a phase diagram of nimodipine. A few crystals of the (+)-antipode are placed on a microscope slide at the edge of a cover glass. The substance is melted. Capillary forces draw the melted enantiomer into the space between microscope slide and cover glass. The amount of substance is chosen such that the melt occupies about half the space between microscope slide and cover glass. The preparation is solidified by cooling and the racemate is treated in the same manner. In the zone where the melts come into contact, enantiomer

Table 1
Physical properties of nimodipine modifications I and II

Modification	Modification I	Modification II
m.p. (°C) DSC onset temperature	124 ± 1 [a]	116 ± 1 [a]
Enthalpy of fusion (kJ mol^{-1})	39 ± 1 [a]	46 ± 1 [a]
Enthalpy of transition (kJ mol^{-1}) [at temperature (°C)] into		7 ± 2 [88 ± 8] → modification I
True density (g cm^{-3})	1.272 ± 0.008 [a]	1.300 ± 0.008 [a]
Calculated density (g cm^{-3})	1.271	1.303
Stability under ambient conditions	metastable	stable
Lab values	$L = 94.3$	$L = 97.0$
	$a = -12.3$	$a = -3.8$
	$b = 29.9$	$b = 7.4$
Solubility (mg per 100 ml)		
In water at 25 ± 0.1°C (elution method)	0.036 ± 0.007 [a]	0.018 ± 0.004 [a]
In water at 37 ± 0.1°C (elution method)	0.086 ± 0.014 [a]	0.044 ± 0.010 [a]
In ethanol at 25 ± 0.1°C (flask method)	– [c]	3988 [b]

[a] 95% confidence interval (five determinations).
[b] Mean of the results of two determinations; confidence interval not stated.
[c] Could not be determined: during the determination modification I transformed into modification II.

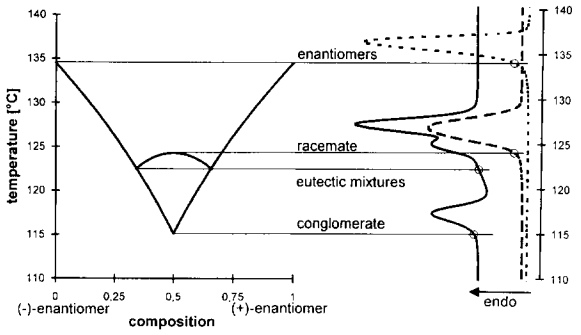


Fig. 1. Phase diagram and DSC thermograms of nimodipine (———) conglomerate, (— — —) racemic compound, (- - - - - -) (−)-enantiomer).

and racemate merge. By heating the preparation again and observing the results, it is possible to construct a qualitative phase diagram. The results of the thermomicroscopic investigations using the contact method demonstrate that, in addition to the conglomerate and racemic compound, another form (eutectic mixture) of nimodipine can be produced. The melting point of the eutectic mixture (+122°C) was 2°C less than that of the racemic compound.

Fig. 1 shows the phase diagram for nimodipine calculated from the melting points and enthalpies of fusion of nimodipine, using the equations of Prigogine-Defay (Jaques et al., 1981b) and Schröder- van Laar (Jaques et al., 1981c). The DSC thermograms (onset temperatures) obtained experimentally correlate very well with the calculated melting points. The thermograms indicate, all told, up to four endothermic peaks: conglomerate +116°C, eutectic mixture +122°C, racemic compound +124°C and the pure optical antipodes at +134°C.

3.2. Spectroscopy

Fig. 2 depicts the IR, Raman and FIR spectra of modifications I and II. There are differences in the lattice vibrations (FIR and Raman). These are due primarily to the various intermolecular

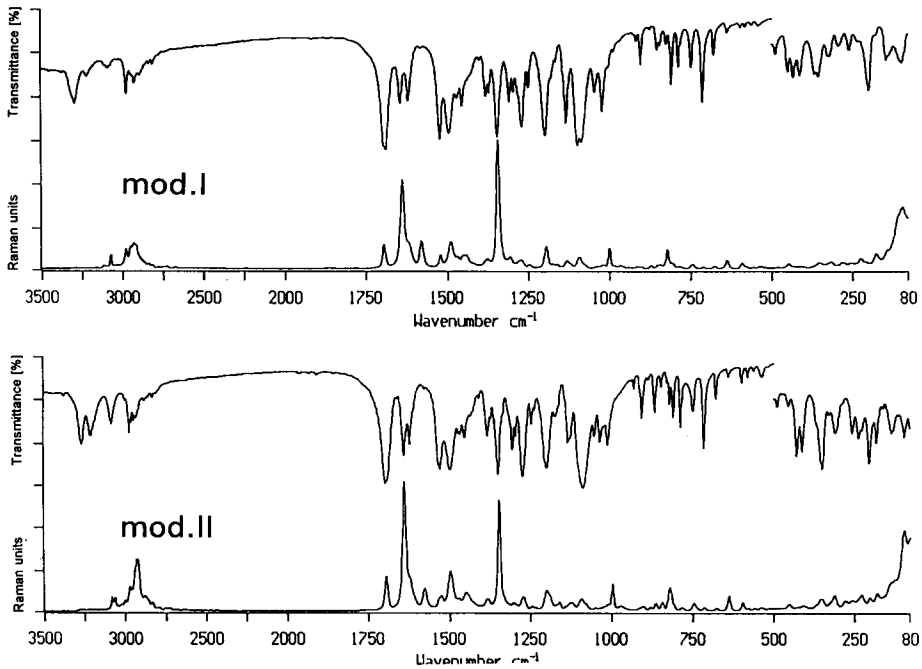


Fig. 2. IR, FIR and Raman spectra of nimodipine modifications I and II.

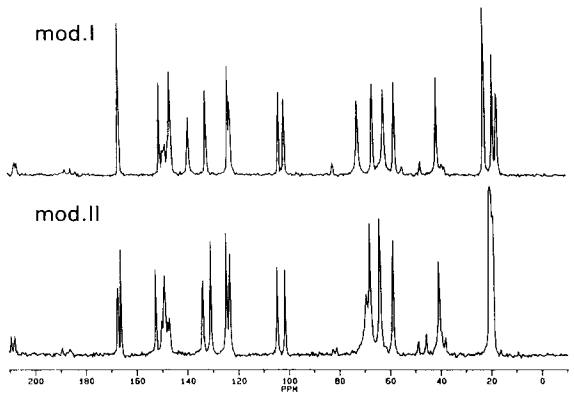


Fig. 3. ^{13}C-NMR spectra of nimodipine modifications I and II.

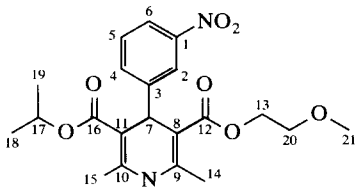
interactions in the modifications. There are also differences between the two polymorphs in respect of the intramolecular vibrations, as can be seen from the IR and Raman spectra.

Fig. 3 shows the CP-MAS spectra of modifications I and II. By virtue of the clear-cut differences in spectra in respect of the chemical shift in the individual signals and in the signal intensity, it is possible to distinguish between the modifications on the basis of the NMR spectroscopy data. Table 2 lists the assignments of the chemical shifts. The ^{13}C-NMR spectrum of nimodipine recorded in $CDCl_3$ is shown for comparison. The spectra show differences in the aliphatic and in the aromatic regions.

3.3. X-ray structure

X-ray structure analysis was used to ascertain the atomic coordinates of the two modifications. The lattice constants are shown in Table 3. The internal coordinates (bond lengths, bond angles

Table 2
Chemical shifts in the ^{13}C-NMR spectra of nimodipine modifications I and II, in the solid state, and in $CDCl_3$ solution



	$CDCl_3$ (ppm)	Modification I (ppm)	Modification II (ppm)
C-1	148.15	150.43	148.86
C-2	123.28	123.39	124.54
C-3	150.09	150.43	152.31
C-4	134.72	139.06	133.82
C-5	128.61	132.13	130.67
C-6	121.28	122.63	123.10
C-7	40.10	47.70	40.76
C-8	103.00	101.26	104.51
C-9	145.38	148.26	147.76
C-10	144.60	146.20	147.01
C-11	103.81	103.31	101.35
C-12	166.62	166.44	166.03
C-13	62.99	62.09	63.95
C-14	19.39	17.46	20.28
C-15	19.54	19.12	20.28
C-16	167.13	166.44	167.29
C-17	67.37	66.45	67.86
C-18	22.12	22.49	20.28
C-19	21.80	22.49	20.28
C-20	70.54	72.36	69.30
C-21	58.83	57.89	58.78

Table 3
Lattice constants of modifications I and II

	Modification I	Modification II
Crystal system	monoclinic	orthorhombic
Space group	$P2_1/C$	$P2_12_12_1$
Z	4	4
a (Å)	13.9261(6)	11.6117(6)
b (Å)	10.9830(6)	12.5724(6)
c (Å)	14.8312(6)	14.6146(6)
α (°)	90	90
β (°)	104.9224(3)	90
γ (°)	90	90

and torsion angles) are shown in Tables 4–6. Fig. 4 and 5 show the molecular geometry of the polymorphs.

Table 4
Internal coordinates of nimodipine modifications I and II as determined by X-ray structure analysis – bond lengths

Atom 1	Atom 2	Length (Å)	
		Modification I	Modification II
O1	N1	1.207(5)	1.222(7)
O2	N1	1.210(4)	1.229(7)
O3	C14	1.208(4)	1.201(6)
O4	C14	1.346(4)	1.354(6)
O4	C19	1.449(5)	1.447(7)
O5	C15	1.213(4)	1.208(6)
O6	C15	1.347(5)	1.346(7)
O6	C16	1.473(5)	1.472(7)
O7	C20	1.412(5)	1.407(7)
O7	C21	1.437(6)	1.47(2)
N0	C9	1.381(5)	1.386(7)
N0	C11	1.380(5)	1.397(7)
N1	C3	1.458(5)	1.478(8)
C1	C2	1.375(5)	1.382(8)
C1	C6	1.381(5)	1.392(8)
C1	C7	1.529(5)	1.532(8)
C2	C3	1.385(5)	1.368(8)
C3	C4	1.365(6)	1.369(9)
C4	C5	1.365(6)	1.380(9)
C5	C6	1.379(5)	1.377(8)
C7	C8	1.524(5)	1.541(7)
C7	C10	1.519(5)	1.516(7)
C8	C9	1.338(5)	1.335(7)
C8	C15	1.457(5)	1.474(7)
C9	C12	1.507(6)	1.513(8)
C10	C11	1.340(5)	1.351(7)
C10	C14	1.452(5)	1.475(8)
C11	C13	1.507(6)	1.489(8)
C16	C17	1.564(15)	1.484(10)
C16	C18	1.572(10)	1.507(10)
C19	C20	1.493(6)	1.488(9)

3.4. Other physical properties

Solubility was determined quantitatively by the flask and elution methods (OECD Guidelines, 1981). To measure solubility by the elution method, the sample is applied to a micro-column packed with inert material, and eluted continuously with a constant volume of solvent until the concentration of substance of interest in the solvent remains constant. To determine solubility by the flask method, saturated solutions are prepared from the samples of interest such that an excess of the solute is present as a sediment. The solutions are stirred in a water bath for 16 hours at a constant temperature. The solution is then filtered through a Millipore filter and the quantity of the substance of interest in solution is determined. As part of the determinations, the modification of the residue was also determined. The results of these investigations are shown in Table 1. The solubility of modification I in water at +25 and +37°C was double that of modification II. The modifications investigated did not transform into a different modification in the period from the start to the end of the determination. It was not possible to determine the solubility of modification I in ethanol at +25°C because it transformed into the thermodynamically stable modification II.

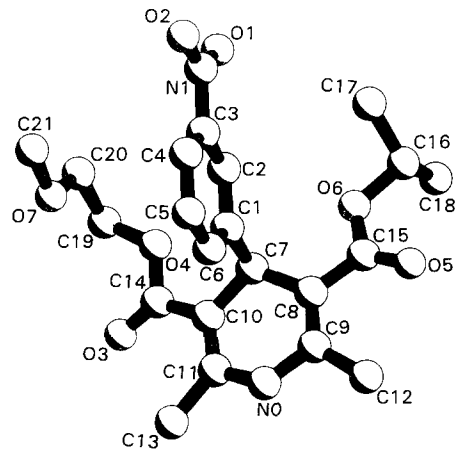


Fig. 4. Molecular geometry of nimodipine modification I.

To determine the thermodynamic transition temperature, suspensions of modifications I and II in various solvents were maintained at various temperatures, whilst stirring, for between 8 and 96 h. The solutions were filtered and the residues

Table 5
Internal coordinates of nimodipine modifications I and II as determined by X-ray structure analysis – bond angles

Atom 1	Atom 2	Atom 3	Angle (°)	
			Modification I	Modification II
C14	O4	C19	119.1(3)	114.8(4)
C15	O6	C16	118.1(3)	116.8(4)
C20	O7	C21	111.7(4)	117.0(1)
C9	N0	C11	123.7(4)	122.6(5)
O1	N1	O2	121.5(5)	123.3(6)
O1	N1	C3	118.3(4)	118.5(6)
O2	N1	C3	120.2(5)	118.2(6)
C2	C1	C6	118.3(4)	117.7(6)
C2	C1	C7	121.1(3)	120.7(5)
C6	C1	C7	120.6(3)	121.6(5)
C1	C2	C3	118.9(4)	120.1(6)
N1	C3	C2	118.7(4)	118.3(6)
N1	C3	C4	118.6(4)	119.0(6)
C2	C3	C4	122.7(4)	122.7(6)
C3	C4	C5	118.4(4)	117.7(6)
C4	C5	C6	119.7(5)	120.4(7)
C1	C6	C5	122.0(4)	121.4(6)
C1	C7	C8	109.5(3)	111.0(4)
C1	C7	C10	111.8(3)	111.4(4)
C8	C7	C10	111.2(3)	110.0(4)
C7	C8	C9	120.7(3)	120.8(5)
C7	C8	C15	118.3(3)	118.4(5)
C9	C8	C15	120.7(4)	120.7(5)
N0	C9	C8	119.2(4)	120.4(5)
N0	C9	C12	112.3(4)	111.6(5)
C8	C9	C12	128.5(4)	128.0(6)
C7	C10	C11	120.4(3)	122.0(5)
C7	C10	C14	118.3(3)	118.7(5)
C11	C10	C14	121.0(3)	119.0(5)
N0	C11	C10	119.5(4)	118.6(5)
N0	C11	C13	112.8(4)	111.8(5)
C10	C11	C13	127.6(4)	129.6(6)
O3	C14	O4	120.7(4)	122.1(5)
O3	C14	C10	127.7(4)	127.5(5)
O4	C14	C10	111.6(3)	110.4(5)
O5	C15	O6	120.9(4)	122.4(5)
O5	C15	C8	127.2(4)	125.5(6)
O6	C15	C8	111.9(4)	112.1(5)
O6	C16	C17	100.6(6)	105.7(6)
O6	C16	C18	105.4(5)	109.6(6)
C17	C16	C18	122.9(9)	114.2(7)
O4	C19	C20	109.0(4)	106.7(5)
O7	C20	C19	109.0(4)	111.3(6)

Table 6
Internal coordinates of nimodipine modifications I and II as determined by X-ray structure analysis – torsion angles

Atom 1	Atom 2	Atom 3	Atom 4	Angle (°)	
				Modification I	Modification II
C19	O4	C14	O3	6.5	8.2
C19	O4	C14	C10	−174.8	−171.6
C14	O4	C19	C20	126.6	163.4
C16	O6	C15	O5	1.8	−1.6
C16	O6	C15	C8	−178.6	177.5
C15	O6	C16	C17	−137.5	−151.9
C15	O6	C16	C18	93.8	85.1
C21	O7	C20	C19	172.2	174.9
C11	N0	C9	C8	11.0	12.8
C11	N0	C9	C12	−168.5	−164.8
C9	N0	C11	C10	−11.1	−11.0
C9	N0	C11	C13	169.8	168.2
O1	N1	C3	C2	−0.1	9.2
O1	N1	C3	C4	178.4	−171.3
O2	N1	C3	C2	179.9	−171.4
O2	N1	C3	C4	−1.6	8.2
C6	C1	C2	C3	0.4	1.2
C7	C1	C2	C3	−177.3	−178.1
C2	C1	C6	C5	−0.2	−0.9
C7	C1	C6	C5	177.6	178.4
C2	C1	C7	C8	111.8	109.4
C2	C1	C7	C10	−124.6	−127.7
C6	C1	C7	C8	−65.9	−69.8
C6	C1	C7	C10	57.8	53.1
C1	C2	C3	N1	178.8	179.2
C1	C2	C3	C4	0.4	−0.3
N1	C3	C4	C5	−179.8	179.6
C2	C3	C4	C5	−1.3	−0.9
C3	C4	C5	C6	1.5	1.1
C4	C5	C6	C1	−0.8	−0.3
C1	C7	C8	C9	101.3	101.6
C1	C7	C8	C15	−73.2	−75.2
C10	C7	C8	C9	−22.7	−22.2
C10	C7	C8	C15	162.8	161.1
C1	C7	C10	C11	−100.1	−99.4
C1	C7	C10	C14	74.8	74.2
C8	C7	C10	C11	22.6	24.1
C8	C7	C10	C14	−162.5	−162.3
C7	C8	C9	N0	7.5	5.5
C7	C8	C9	C12	−173.1	−177.3
C15	C8	C9	N0	−178.2	−177.8
C15	C8	C9	C12	1.2	−0.7
C7	C8	C15	O5	166.2	172.4
C7	C8	C15	O6	−13.3	−6.7
C9	C8	C15	O5	−8.3	−4.3
C9	C8	C15	O6	172.2	176.6
C7	C10	C11	N0	−7.3	−9.1
C7	C10	C11	C13	171.7	171.8
C14	C10	C11	N0	177.9	177.3
C14	C10	C11	C13	−3.1	−1.8

Table 1 (continued)

Atom 1	Atom 2	Atom 3	Atom 4	Angle (°)	
				Modification I	Modification II
C7	C10	C14	O3	174.6	172.9
C7	C10	C14	O4	−4.0	−7.4
C11	C10	C14	O3	−10.5	−13.3
C11	C10	C14	O4	170.9	166.4
O4	C19	C20	O7	−70.3	75.0

dried in a vacuum at room temperature. For temperatures below 80°C the residues show modification II, at 95°C modification I.

UV-Vis spectra of the two modifications dissolved in methanol were recorded. No absorption occurred between 450 nm and 800 nm. There was no difference between the solutions of the two modifications in respect of the UV-Vis spectra. Table 1 shows the Lab values of the two modifications. The Lab value is an indication of the brightness and colour of a substance (Bureau Central de la Comission Electrotechnique Internationale, 1989). Table 1 also shows the densities as measured and as calculated from the results of the X-ray structure analyses.

4. Discussion

Nimodipine crystallizes into two polymorphs. Modification I melts at +124°C ($\Delta H = 39$ kJ mol^{-1}) and modification II at +116°C ($\Delta H = 46$ kJ mol^{-1}). The two forms can co-exist at room temperature. No transformation of the solvent-free modifications had occurred after storage for 1 year at −40, +25 and +50°C, and at a pressure of 9 kbar. The presence of traces of solvent (e.g., isopropanol or ethanol) accelerates the transformation of the thermodynamically metastable modification I into modification II, which is stable at room temperature. Modification I crystallizes from solutions as hexagonal prisms and modification II crystallizes as rectangular prisms.

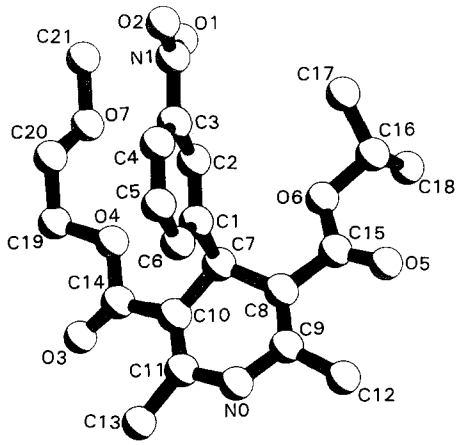


Fig. 5. Molecular geometry of nimodipine modification II.

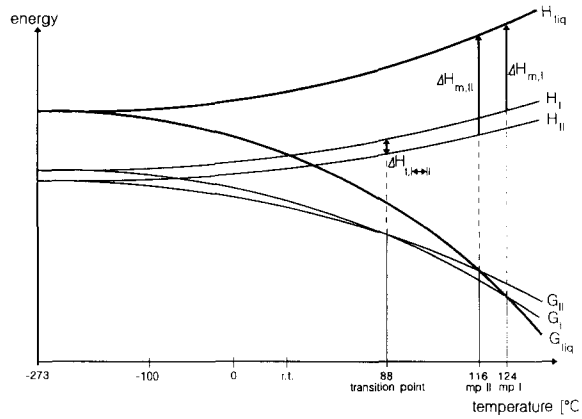


Fig. 6. Energy/temperature diagram for nimodipine.

The modifications differ in colour: modification I is yellow and modification II is almost white. In solution, the two forms exhibit an identical UV-Vis spectrum, so the colour difference is a property of the modifications in the solid state; it is not due to the presence of different concentrations of coloured by-products. The difference in the position of the nitro group relative to the phenyl ring may explain the difference in the appearance of the two modifications. The angle of the NO_2 group to the phenyl ring is 1° in modification I and 9° in modification II. As a result of the almost planar structure of the phenyl ring and of the nitro group, the chromophore of modification I is larger than that of modification II.

The modifications crystallize in primitive monoclinic (modification I) and orthorhombic (mod-

ification II) unit cells. Modification I (molecular geometry shown in Fig. 4) crystallizes in a centrosymmetrical space group with optical antipodes, which in the crystal lattice are present in a ratio of 1:1; this is a racemic compound. In contrast, modification II (molecular geometry shown in Fig. 5) crystallizes in a space group with no mirror planes. The unit cell contains only molecules of one optical antipode, hence modification II crystallizes as a conglomerate. The results of structure analysis of modification I are consistent with published data (Wang et al., 1989). In both polymorphs, the conformation of the dihydropyridine ring is slightly boat-shaped. In both modifications, the dihydropyridine ring and phenyl ring are perpendicular to one another. The nimodipine modifications also differ from one another in respect of the intramolecular conformations of the methoxyethyl ester groups.

Both forms crystallize in continuous chains of one antipode. In the crystals of modification I, the chains of the enantiomers alternate. In both polymorphs there is heteromolecular hydrogen bonding between the NH group of the dihydropyridine ring and the ether oxygen O7; this hydrogen bonding is stronger in modification II. The greater stability of this H bonding may explain why modification II is less soluble than modification I.

With the aid of heat, it is possible to dissolve nimodipine in a number of commonly used solvents of different polarities. Crystallization from a variety of solvents produces, in the main, mixtures of modifications. Pure modification II is obtained when a saturated solution in isopropanol, in which an excess of solute is present as a sediment, is stirred at room temperature for 1 day. At +25 and +37°C, the solubility of modification I in water is double that of modification II. We attribute this to the stronger hydrogen bonding between the NH group and the ether oxygen in modification II. In modification I the H ··· O hydrogen bond is 2.15 Å, i.e. about 0.28 Å longer than that in modification II.

An enantiomeric mixture is a specific type of binary mixture, so this melting behaviour can be depicted by a phase diagram (Fig. 1). In the phase diagram, the melting point of an enantiomeric mixture is plotted as a function of mole fraction. Pure enantiomers the mole fraction is 0 or 1. If it is a racemate the mole fraction is 0.5. If the pure enantiomer is contaminated with an optical antipode the melting point is depressed. At a mole fraction of 0.34, the mixture of the two forms is a eutectic. Between 0.34 and 0.5 the melting characteristics depend on the form of crystallization of the antipodes. If the enantiomeric mixtures form a conglomerate the melting point depresses as a function of the mole fraction. It reaches a minimum when the mixture is racemic. If a racemic compound is formed, after the eutectic point the melting point rises again, reaching a local maximum when the mole fraction is 0.5.

Nimodipine is a racemate. From the temperature scale at a mole fraction of 0.5, the melting characteristics can be inferred directly from the phase diagram. A mixture of the two modifications usually exhibits three endothermic peaks. First the conglomerate melts at +116°C (modification II, 1st peak in the DSC thermogram), followed by recrystallization (exothermic reaction after the 1st fusion peak). The eutectic melts at +122°C (2nd endothermic peak) and the racemic compound at +124°C (3rd endothermic peak, modification I). The supplementary peak at +122°C is not caused by an additional modification.

In a conglomerate, the individual crystals are of pure enantiomers. If the coarse crystals are not mixed homogeneously, the sample may not be a racemate; the enantiomers may be present in a different proportion. It is clear from the phase diagram that the melting behaviour of a mixture with another mole fraction is different. In extreme cases, only one enantiomer is present (melting point +134°C). This is the case if the sample is a large single crystal.

From the results of thermal analysis reported here, and from the results of the solubility and density determinations, it is possible to draw a semi-schematic energy/temperature (ET) diagram (Burger and Ramberger, 1979a) for the two forms and the melt (Fig. 6). It shows the theoretical profile of the isobars of enthalpy H and of the free enthalpy G of modification I, modification II

and of the melt (liquidus curve). The relationship between the G and H curves is expressed by the Gibbs-Helmholtz equation:

$$G = H - TS$$

where T is the absolute temperature and S the entropy. The ET diagram furnishes a great deal of information, including information about the thermodynamic stability and transformation characteristics. The position of the G curves characterizes thermodynamic stability. At a given temperature, the form with the lower free enthalpy is the thermodynamically stable form. The intercept of the G curves ($\Delta G = 0$) represents a thermodynamic transition point. The ET diagram shows that the G isobars of modification I and modification II intersect. The two modifications are enantiotropic. Both are able to undergo reversible transformation into the other at the thermodynamic transition point. Applying the density rule (Burger and Ramberger, 1979b), it follows that modification II is thermodynamically stable from −273°C to the transition point, modification I is thermodynamically stable from the transition temperature to the melting point (+124°C) and the melt is thermodynamically stable above +124°C.

The next equation shows the relationship between the solubility of the modifications and thermodynamic stability:

$$\Delta G = RT\ln(C_1/C_2)$$

where R is the gas constant, T denotes the absolute temperature and C_1 and C_2 are the solubilities of the two modifications. At a given temperature, the thermodynamically stable form is less soluble than the metastable form. At +25 and +37°C, modification II is only half as soluble as modification I. Thus, modification II has greater thermodynamic stability. When a suspension of the substance in solvent is stirred at temperatures between room temperature to +80°C, modification I transforms into modification II. At a temperature of +95°C, the transition behaviour is reversed and modification II transforms into modification I. There is a dynamic equilibrium between the sediment, i.e., the excess solute, and the solution. That is to say, the processes of dissolution and crystallization result in a constant exchange of substance between sediment and solution. During this process the substance crystallizes into the modification which is thermodynamically stable at that temperature. An example is the determination of solubility of the polymorphs in ethanol (Table 1). During the investigation modification I transformed into modification II, which is thermodynamically stable at +25°C. Nimodipine is very soluble in ethanol and this fact increases the likelihood that transformation will occur. The results of the solubility determinations demonstrate that the thermodynamic transition point is between +80 and +95°C. The transition temperature as determined experimentally is consistent with the theoretical profile of the G isobars in the ET diagram. The transition enthalpy of the reversible transformation from modification I to modification II, which has not yet been determined directly, can be estimated from the difference in the H isobars as about 7 kJ mol^{-1}.

The thermodynamic metastability of modification I leads to physical instabilities of formulations of nimodipine in this crystal form. The instability occurs primarily when the product is stored at elevated temperature or for a prolonged period, impairs the efficacy and safety of this product. It is therefore very important to use as stable a suspension as possible in the manufacture of drug products which contain nimodipine.

As the results of our study show, modification II is the thermodynamically stable crystal form at ambient conditions. It is very suitable for the manufacture of stable and storable pharmaceutical preparations which contain nimodipine crystals, especially for suspensions.

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