Polymorphism of Racemic Felodipine and the Unusual Series of Solid Solutions in the Binary System of its Enantiomers

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ABSTRACT: The aim of this study was to investigate the binary phase diagram and the polymorphism and pseudopolymorphism of racemic and enantiomeric felodipine, including their spectroscopic and thermodynamic properties. Different crystal forms were obtained by crystallization from solvents or from the annealed melt and investigated by thermal analysis (hot stage microscopy, differential scanning calorimetry, thermogravimetric analysis), spectroscopic methods (Fourier transform infrared–and Fourier transform–Raman spectroscopy), and X-ray powder diffractometry. The binary melting phase diagram was constructed based on thermoanalytical investigations of quantitative mixtures of (+)- and (±)-felodipine. Two polymorphic forms of racemic felodipine, mod. I (mp, ~145°C) and mod. II (mp, ~135°C), as well as an acetone solvate (S_{Ac}) were characterized. Melting equilibria of felodipine crystal forms decrease due to thermal decomposition. Enantiomeric felodipine was found to be dimorphic (En-mod. I: mp, ~144°C; En-mod. II: mp, ~133°C). Evaluation of the binary system of (+)- and (−)-felodipine results in the formation of a continuous series of mixed crystals between the thermodynamically stable and higher melting modifications, mod. I and En-mod. I. Their unusual curve course, termed as Roozeboom Type 2 b, passes through a maximum in the racemic mixture and is flanked by a minimum at 20% and at 80% (+)-felodipine. From the thermodynamic parameters, racemic mod. I and II are monotropically related. In contrast to S_{Ac}, the thermodynamically unstable mod. II shows a considerable kinetic stability. Because its crystallization is badly reproducible, the use of mod. II is not advisable for processing. However, desolvation of S_{Ac} leads to a profitable crystal shape of mod. I, representing a pseudoracemate by definition. J Pharm Sci 90:949–959, 2001

Keywords: dihydropyridine; polymorphism; thermal analysis; phase diagram; enantiomers; solid solutions; pseudoracemate

INTRODUCTION

Dihydropyridine calcium channel blockers (DHP) represent a group of cardiovascular drug substances that is widely used in the treatment of hypertension and angina pectoris.[1] Among them, the phenomenon of polymorphism and pseudopolymorphism is frequently observed, as previous papers demonstrate (felodipine,[2] nifedipine,[3] nimodipine,[4] or nitrendipine[5,6]. Because neglecting this behavior of crystallizing in different crystal forms results in unforeseen problems in pharmaceutical manufacture, it is of high analytical, technological, and economic interest to reveal the existence of polymorphism and to evaluate the stability and physicochemical characteristics of the different crystal forms.[7,8]

In addition to their inclination to polymorphism, all DHPs currently approved for use in man, except for nifedipine and lacidipine, are chiral molecules because of an asymmetric substitution of ester groups in position 3 and 5 of the DHP ring (Figure 1). The chiral center is in position 4.

No indication concerning polymorphism is given in the monograph of felodipine in the European Pharmacopoeia 1997. However, in

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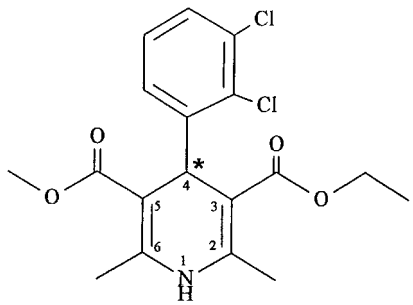

Figure 1. Chemical structure of felodipine (the asterisk marks the chiral center of the molecule).

1992, Srčič and co-workers published a report on its polymorphism.[2] Therein three modifications are stated (mp 144.9, 141.4, and 133.9°C) as well as their observation of two additional polymorphic forms obtained by recrystallization of glassy felodipine (mp 137.8 and 147°C). Further references to melting points range between 140 and 145°C.[9–11] In 1989, Lamm and Simonsen published the melting points of *S*- and *R*-felodipine with mp values of 145.3 and 145.4°C, respectively.[12] In addition, they deduced the absolute configuration of the enantiomers on esterification with (*R*)-mandelic acid by X-ray crystallography. The *S*-(−)-form is the pharmacologically active enantiomer of the commercially available racemate (i.e., Munobal®, Plendil®).[13]

The specific aims of this work are to characterize the crystal forms involved in the binary system of (+)- and (−)-felodipine by a thermoanalytical and spectroscopic investigation of felodipine enantiomers and their mixtures, including the racemic mixture. By means of the construction of the phase diagram, the racemate type(s) of racemic modifications are determined. Furthermore, physicochemical properties and thermodynamic aspects of investigated crystal forms will help to clarify their practical and analytical relevance. A possible connection between polymorphism and melting point deviations given in the literature is investigated.

MATERIALS AND METHODS

Racemic felodipine INN, ethyl methyl 1,4-dihydro-2,6-dimethyl-4(2,3-dichlorophenyl)-3,5-pyridinedicarboxylate (Figure 1; $C_{18}H_{19}Cl_2NO_4$; M_r 384.3), as well as the respective enantiomers (optical purity, 99.5%) were provided by Solvias AG, Basel, Switzerland. All solvents and chemicals used for this study were of analytical grade.

Thermoanalysis

Hot stage microscopy was performed using a Reichert-Thermovar polarizing microscope fitted with a Kofler hot-stage (Reichert, Vienna, Austria). Additionally, a Kofler hot-bench (Reichert, Vienna, Austria) was used for preparing crystal films.

Differential scanning calorimetry (DSC) was carried out with a DSC-7 (Perkin-Elmer, Norwalk, CT) using the Pyris Software Ver. 2.0 for Windows. Sample masses for quantitative analysis were 1–3 mg ± 0.0005 mg (Ultramicroscales UM3, Mettler, CH-Greifensee, Switzerland) weighed into perforated aluminum sample pans (25 μL). Nitrogen 5.0 (20 mL min^{-1}) was used as purge gas. The temperature axis was calibrated with benzophenone (mp 48.0°C) and caffeine (mp 236.2°C). Enthalpy calibration of the DSC signal was performed with indium 99.999% (Perkin-Elmer, Norwalk, CT). The normal heating rate (HR) was 5 K min^{-1}.

Thermogravimetry (TG) was carried out with a TGA-7 instrument (Perkin-Elmer, Norwalk, CT); 50-μL platinum sample pans were used and purged with nitrogen 5.0 (balance purge: 40 mL min^{-1}; sample purge: 20 mL min^{-1}). The sample weight was ~1–5 mg±0.0005 mg and the heating rate was 5 K min^{-1}. Mass calibration was performed with a 100.0-mg calibration weight (Perkin-Elmer), and temperature calibration was performed with alumel (magnetic transition temperature 163.0°C) and nickel (magnetic transition temperature 354.0°C).

X-ray powder diffraction (XRPD) patterns were obtained on a Siemens D-5000 X-ray diffractometer equipped with θ/θ-goniometer (Siemens AG, Karlsruhe, Germany) using monochromatic CuK_α radiation (tube voltage, 40 kV; tube current, 40 mA) from 2 to 40° 2θ at a rate of 0.005° 2θ s^{-1}. The diffractometer was fitted with a Göbel mirror (entrance slit, 1 mm; exit slit, 0.6 mm) and a scintillation counter (Soller slit; detector slit, 0.1 mm). The idealized X-ray powder pattern for a CuK_α radiation was calculated using the program *PowderCell for Windows*.[14]

Fourier transform infrared (FTIR) spectra were recorded with a Bruker IFS 25 FTIR-spectrometer (Bruker Analytische Messtechnik GmbH, Karlsruhe, Germany) connected to a Bruker FTIR-microscope (15× Cassegrain-objec-

tive and visible polarization). Samples were scanned as potassium bromide pellets (diameter 13 mm; 1 mg felodipine to 270 mg potassium bromide; pressure 740 MPa) at an instrument resolution of 2 cm^{-1} in the spectral range from 4000 to 600 cm^{-1} (50 interferograms per spectrum). For FTIR microscopy, small samples were rolled on a zinc selenide window (13 × 2 mm) and recorded at an instrument resolution of 4 cm^{-1} (focus diameter 50 μm, 100 interferograms per spectrum).

Fourier transform–Raman (FT–Raman) spectra were recorded with a Bruker RFS 100 FT-Raman spectrometer (Bruker Analytische Meßtechnik GmbH, Karlsruhe, Germany) equipped with a diode-pumped 100 Nd:YAG laser (1064 nm) as the excitation source and a liquid nitrogen-cooled high-sensitivity detector. The powder samples were packed into small aluminum cups, and the spectra were recorded at an output power of 200 mW (64 scans at 4 cm^{-1} instrument resolution).

Polarimetry

Optical rotation was measured with a Perkin Elmer Polarimeter 341 (Überlingen, Germany) using the microcell (pathlength 100 mm, volume 1 mL). Measurements were carried out at 20°C, wavelength 589 nm. 2-Propanol/*n*-hexane (27:20) was used to prepare 0.4% solutions of (−)-felodipine. Specific rotation ($[\alpha]_D^{20}$) was calculated as:

$$[\alpha]_D^{20} = \frac{100\alpha}{LC} \quad (1)$$

where α is the instrument reading, L is the length of the cuvette, and C is the weight percent of solute in the solution. In addition, a solution was prepared with molten (−)-felodipine (2 min at 150°C) as already described. Its specific rotation did not deviate significantly, indicating that a racemization of felodipine enantiomers through melting could be excluded.

High-performance liquid chromatography (HPLC) was performed with an HP 1100 liquid chromatograph equipped with an ultraviolet (UV) detector (HP G1314A VWD), an automatic injector, an autosampler, a column oven, and a printer (Hewlett-Packard, Waldbronn, Germany). The detection wavelength was 254 nm. Compounds were separated on a LiChroCART® 125-4, LiChrospher® RP-18 column (particle size 5 μm; Merck, Darmstadt, Germany) with the solvent mixture phosphate buffer (pH 3.0)/methanol/acetonitrile (40:20:40) at a flow rate of 1 mL min^{-1}. Sample preparation was carried out according to the felodipine monograph in the European Pharmacopoeia 1997. The injection volume was 20μL. All experiments were performed at room temperature.

RESULTS

Preparation and Thermoanalysis of Racemic Crystal Forms

Three different crystal forms of (±)-felodipine were gained by crystallization from different solvents. Table 1 gives an overview of their most important physicochemical properties.

The crystal form of the commercial batch is the highest melting and solvent-free mod. I. It is easily obtained by crystallization from the majority of solvents (methanol, ethanol, 1- and 2-propanol, etc.) as transparent, whitish grains and rods of different size. Mod. II crystallized best at room temperature from *n*-hexane/methanol (10:1) in a closed, nuclei-free atmosphere, but shows poor reproducibility. The colorless crystals of mod. II consist of small hexagonal platelets. The crystallization of both modifications side by side may be achieved on the object slide if the melt is quenched on a metal block and annealed at 80–100°C for at least 4 h. As shown in Figure 2, their crystal film can easily be distinguished by their different birefringence. On reheating this crystal film of mod. I and II, the initiation of the melting process decreases by ~3–5 K.

An acetone solvate (S_{Ac}) of (±)-felodipine is quantitatively achieved from a stirred suspension of mod. I in acetone (magnetic stirrer, 900 rotations per minute, ambient condition). Depending on crystal formation of S_{Ac} (experimental values lie between 10 min and 5 h), an abrupt and complete transition takes place. Crystallization from the hot saturated solution of felodipine in acetone at room temperature results in a mixture of mod. I and S_{Ac}. By hot-stage microscopy, the following processes, starting with S_{Ac}, were observed. The transparent rods of ~50-μm length desolvate during heating at ~55°C and transform into mod. I. The remaining S_{Ac}, which is not desolvated, inhomogeneously melts at ~70°C. At the same time, tiny needles and prisms of mod. I crystallize and finally melt between 140 and 144°C. The DSC trace showing the aforementioned processes and the TG curve of

Table 1. Physicochemical Data of (±)- and (+)- Felodipine Crystal Forms

	(±)-Felodipine			(+)-Felodipine	
Crystal form	Mod. I	Mod. II	S_{Ac}	En-mod. I	En-mod. II
Preparation by crystallization	from methanol or ethanol	from *n*-hexane/methanol (10:1)	from a supension of mod. I in acetone	Crystallization from solvents	Crystallization by slow evaporation of solvent
mp TM (°C)	141–146	131–135	~70	141–145	132–134
DSC (Onset,°C)	143.0	130.6	~70	141.0	—
DSC (Peak,°C)	145.5	135.2	~75	144.0	—
Enthalpy of fusion (kJ mol^{-1})	31.5±0.2[a]	26.7 ± 0.2[a]	~43[b]	25.4 ± 0.2[a]	—
Entropy of fusion (J mol^{-1}K^{-1})	75.3±0.5[a]	65.4±0.5[a]	—	60.8 ± 0.4[a]	—
Specific rotation $[\alpha]_D^{20}$(°)	—	—	—	+ 5.6	—
Mass loss between 25 and 160°C (%)	< 0.1	< 0.1	12.8–13.2	< 0.1	< 0.1
Characteristic wavenumbers of FTIR spectra (cm^{-1})	3371	3336	3332	3371	3343
	2980	2982	2982	2979	2987
	2949	2948	2946	2947	2950
	1699	1699	1705	1699	1701
	1686	1683	1696	1686	—
	1645	1652	1640	1644	1655
	1622	1622	1616	1621	—
	—	—	—	—	1529
	1496	1505	1496	1498	1487
	1307	1307	1309	1307	1346
	1278	1284	1274	1278	1299
	1116	1118	—	1115	1122
	1099	1101	1095	1098	1101
	802	807	797	802	808

[a] 95% confidence interval.
[b] Enthalpy of fusion and desolvation.
Measured in 2-propanol/*n*-hexane (27:20); $c = 0.4\%$; λ, 589 nm.

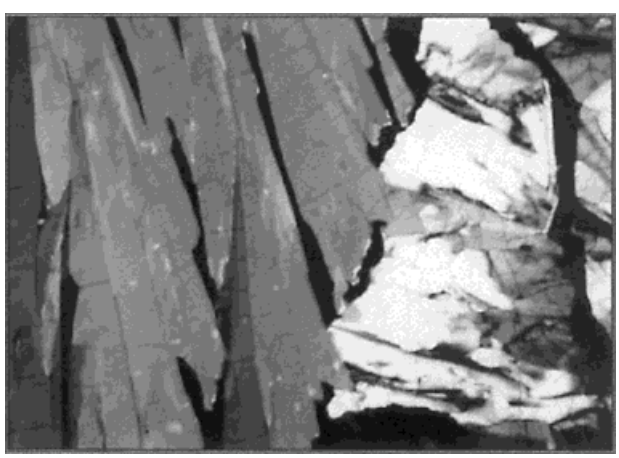

Figure 2. Micrograph with polarized light (1 cm ≈ 100 μm): crystal film of (±)-felodipine mod. I (left) and mod. II (right).

S_{Ac} are depicted in Figure 3a. Whereas mod. I and II show no significant mass loss on heating, S_{Ac} loses a mass of 12.8 to 13.1% between 50 and 80°C. This amount corresponds to one molecule acetone per molecule felodipine (stoichiometric: 13.13% mass loss). The crystal shape of mod. I gained by desolvation of S_{Ac} after storage at ambient conditions for 3 days is characterized by a high surface area. Therefore, it strongly differs from those crystals obtained by crystallization from organic solvents.

The DSC traces of mod. I and II, crystallized from solvents are depicted in Figure 3b and 3e, respectively. These traces show single endothermic melting peaks. The respective heats of fusion were determined from at least three runs and are summarized with further DSC data in Table 1. Although no solid–solid transition of mod. II into I

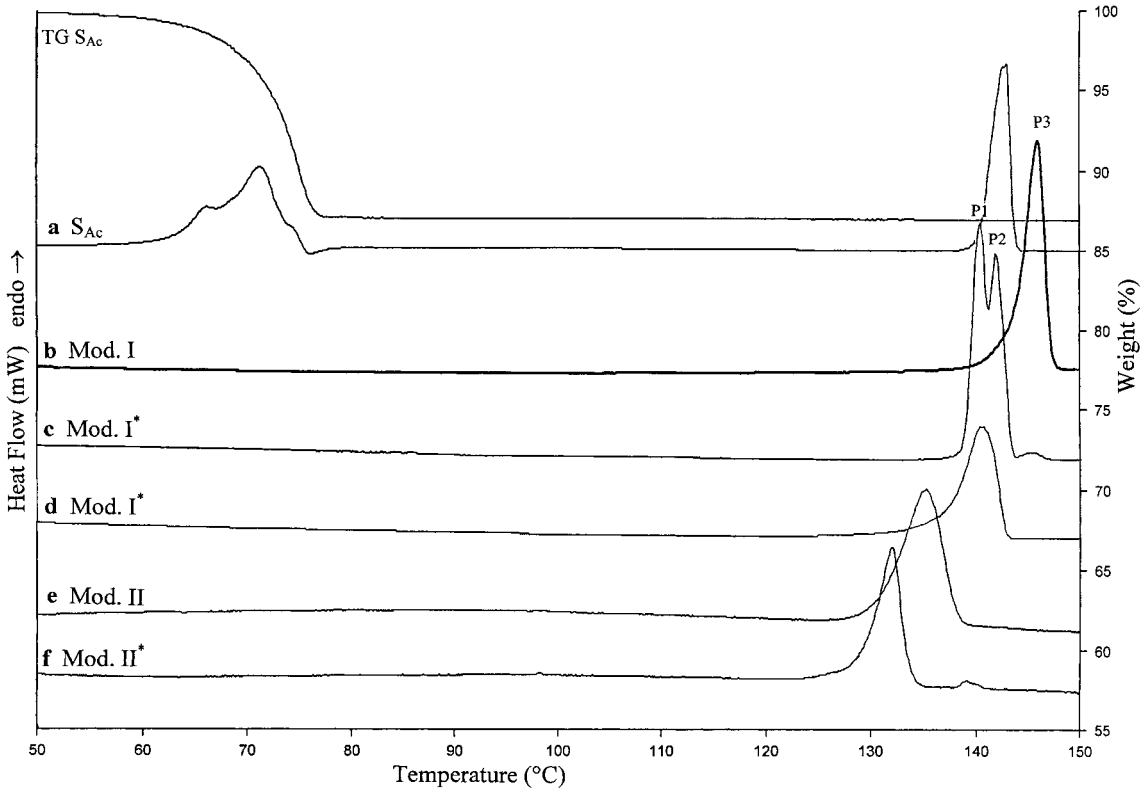

Figure 3. DSC traces of (±)-felodipine crystal forms: (**a**) S_{Ac}, inclusive TG; (**b**) Mod. I (first run); (**c**) Mod.I*(obtained by annealing the melt at 100°C, 30 min, seeded with mod. I); (**d**) Mod.I* (obtained by annealing the melt at 90°C, 16 h); (**e**) Mod.II [crystallized from *n*-hexane/methanol (10:1)]; (**f**) Mod.II* (obtained by annealing the melt at 90°C, 16 h).

could be observed, a heat of transition ($\Delta_{trs}H_{II\rightarrow I}$) of -4.8 kJ mol^{-1} can be estimated from the heat of fusion difference ($\Delta_{trs}H_{II\rightarrow I} = \Delta_{fus}H_{II} - \Delta_{fus}H_{I}$) in the range before melting temperature.

Formation of Decomposition Products

The melting peaks of recrystallized mod. I and II (labeled with I* and II* in Figure 3d and f, respectively), obtained by annealing the melt at 90°C for 16 h, decrease by ~5 K. Their heats of fusion diminish by almost 20%. The probable existence of further modifications, as stated in the literature[2] and that could be the reason for the decreased melting peaks, was examined in detail. The fact that FTIR spectra and XRPD patterns of mod. I and I*, as well as those of mod. II and II*, are not distinguishable is an indication for no further modifications. In addition, proceeding from mod. I* or II*, no crystallization into the higher melting mod. I or II, respectively, could be obtained. In Figure 3c, the melt of felodipine was seeded with mod. I to induce its crystallization and then annealed at 100°C for 30 min. The DSC trace of this recrystallized sample also shows melting peaks (Figure 3c, P1 and P2), which clearly lie below the melting peak of felodipine mod. I (P3). Whereas the scale of formation of the decomposition product is too small to be detectable by FTIR spectroscopy or XRPD, it is clearly manifested in the DSC trace. Depending on the temperature and time at which the samples were stored for crystallization on the hot bench, more or less formation of a high melting decomposition product could be detected, which causes an eutectic melting with felodipine (P1) at 137°C. P2 represents the end of melting of the component in excess. An analogous behavior was found for mod. II. In addition to the thermoanalytic investigations, the decomposition of felodipine in the molten state was detected by HPLC. According to the monograph of the European Pharmacopoeia 1997, felodipine impurity A [i.e., ethyl methyl 2, 6-dimethyl-4(2,3-dichlorophenyl)-3,5-pyridine-dicarboxylate (dehydrofelodipine)], was identified in molten and annealed samples, but not in the

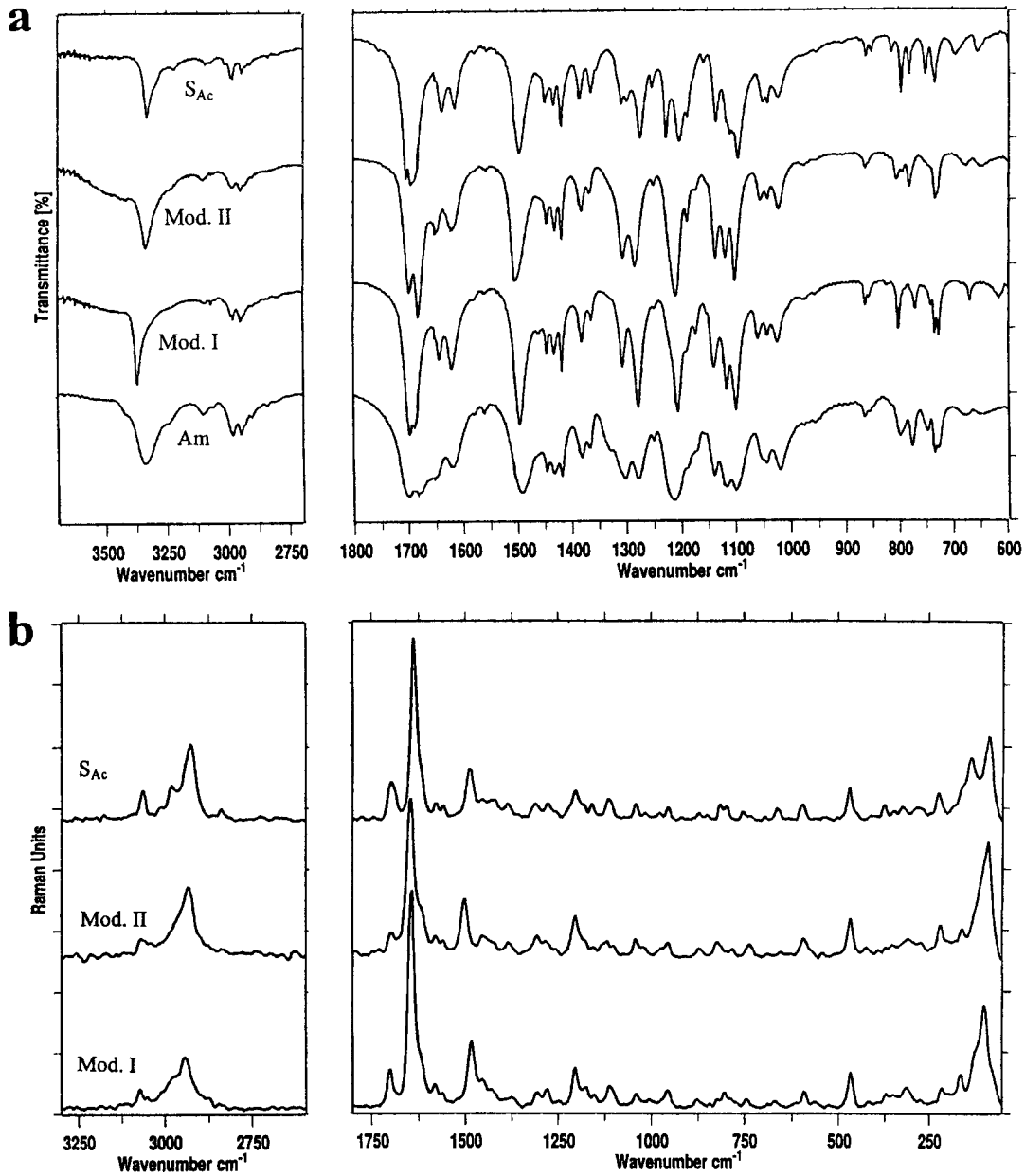

Figure 4. (**a**) FTIR spectra of (±)-felodipine crystal forms and the amorphous state (KBr pellets); (**b**) FT–Raman spectra of (±)-felodipine crystal forms; (**c**) measured XRPD patterns of (±)-felodipine crystal forms, and calculated powder pattern from single-crystal structure analysis.[15]

commercial product. In this way, it was concluded that these lower appearing melting peaks (I* and II*) do not indicate new crystal forms. They can be assigned to impure mod. I and II, respectively.

Vibrational Spectroscopy and X-ray Powder Diffractometry of Racemic Crystal Forms

The FTIR spectra of the racemic crystal forms of felodipine and its supercooled melt are depicted in Figure 4a. All forms showed sufficient kinetic stability to record their spectra with KBr pellets. The most characteristic frequencies are given in Table 1. The greatest difference between the spectra of the two modifications are related to the first absorption band. Compared with mod. I, this N–H stretch of mod. II is shifted to lower wavenumbers (3371 versus 3336 cm^{-1}). As can be seen in Table 1 and Figure 4a, there are also absorption differences in the fingerprint region of

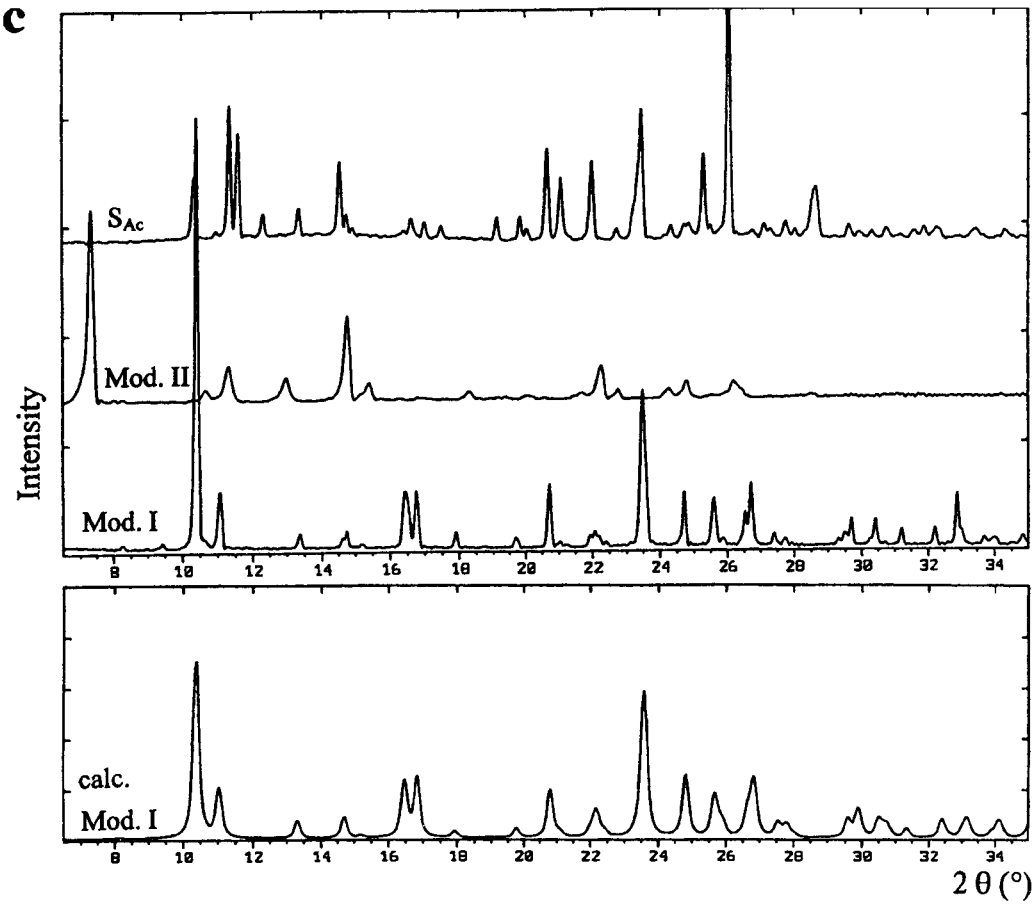

Figure 4. (*Continued*)

mod. I and II. Otherwise, only small shifts and intensity changes can be observed. However, S_{Ac} shows a very similar N–H stretching band to that of mod. II, but is easily distinguishable from the other forms by clear differences below wavenumber 1310 cm^{-1}. As expected, the bands of the amorphous solid are broadened over the whole spectral range.

The FT–Raman spectra of the three crystal forms of racemic felodipine are shown in Figure 4b. Small but significant differences can be found in the range of aromatic and aliphatic C–H stretching bands between 3080 and 2900 cm^{-1} (mod. I: 3073 cm^{-1}; mod. II: 3071 cm^{-1}; and S_{Ac}: 3065 cm^{-1}), as well as in the range of C=O and C=C stretching vibrations (mod. I: 1643 cm^{-1}; mod. II: 1648 cm^{-1}; and S_{Ac}: 1640 cm^{-1}). In the region of 1500 cm^{-1}, the aliphatic bending vibrations show unique shifts for each of the three crystal forms (mod. I: 1484 cm^{-1}; mod. II: 1503 cm^{-1}; and S_{Ac}: 1490 cm^{-1}). In addition, the lattice vibration below 250 cm^{-1} clearly indicates three different crystal lattices.

The XRPD patterns of mod. I, II, and S_{Ac} are compiled in Figure 4c. These patterns show distinct differences in positions and relative intensities that are listed in Table 2. Therefore, XRPD represents an essential analytical tool for the characterization and identification of these three crystal forms. For the assignment of the X-ray single-crystal structure of felodipine ($P2_1/c$) published by Fossheim in 1986,[15] the powder pattern was calculated from crystal structure data as recommended by Bar and Bernstein.[16] The computed diffractogram is added to the measured patterns in Figure 4c. In this way, a correlation of the generated with the measured diffractogram of mod.I is clearly visible.

Identification and Characterization of Enantiomeric Crystal Forms (En-mod)

Only small quantities of (+)- and (–)-felodipine (11 and 6 mg, respectively) were available for investigation; from these amounts, two modifications could be identified. En-mod. I crystallizes

Table 2. Two Theta Positions (2θ), *d* Spacings (*d*) and Relative Intensities (*I*) of X-ray Powder Diffraction Pattern of (±)-Felodipine Crystal Forms

Mod. I			Mod. II			S_{Ac}		
2θ (°)	*d* (Å)	*I*(%)	2θ (°)	*d* (Å)	*I*(%)	2θ (°)	*d* (Å)	*I*(%)
10.43	8.48	100.0	7.36	12.0	100.0	10.35	8.54	25.5
11.06	7.99	13.0	10.68	8.28	6.6	11.36	7.79	52.3
13.36	6.62	4.4	11.33	7.80	19.6	11.60	7.62	42.7
14.73	6.01	4.6	13.00	6.80	12.8	12.32	7.18	11.9
16.47	5.38	13.3	14.78	5.99	44.8	13.34	6.63	14.0
16.77	5.28	12.8	15.42	5.74	9.3	14.55	6.08	31.0
17.92	4.95	4.3	18.32	4.84	5.3	16.63	5.33	11.0
20.74	4.28	13.3	20.09	4.42	3.4	19.12	4.64	10.4
22.10	4.02	4.0	21.70	4.09	3.7	19.85	4.47	11.5
23.51	3.78	31.3	22.28	3.99	16.6	20.68	4.30	34.7
24.72	3.60	11.3	22.78	3.90	5.8	21.07	4.21	23.9
25.62	3.47	10.4	24.28	3.66	5.7	22.00	4.04	28.6
26.72	3.33	13.2	24.82	3.58	8.1	23.46	3.80	47.0
29.70	3.01	5.9	26.25	3.39	8.5	25.30	3.52	36.3
30.43	2.94	5.7	26.44	3.37	5.7	26.06	3.42	100.0
32.91	2.71	9.4	—	—	—	28.62	3.12	21.9

from solvents and from the annealed melt. In contrast to the racemic crystal forms, the melting process of En-mod. I is hardly diminished on reheating. Therefore, the thermal stability of felodipine enantiomers is assumed to be higher than that of the racemate.

En-mod. II was gained by slow evaporation of different solvents at ambient conditions. This handling leads to a glassy state of felodipine with crystal seeds of En-mod. II. Its crystallization requires a few days and is often suppressed by crystals of the faster growing En-mod. I. No further thermoanalytical investigations were carried out with En-mod. II because of its instability.

The enantiomeric modifications were prepared on a zinc selenide window and spectra were recorded by FTIR microscopy. The spectra of the two racemic and the two enantiomeric modifications are compiled for a better comparison in Figure 5 (characteristic frequencies in Table 1). The FTIR spectrum of En-mod. II clearly differs from those of the other crystal forms in the whole spectral range. However, En-mod. I displays a pattern closely resembling that of racemic felodipine mod. I. In the same manner, their XRPD patterns demonstrate no substantial differences (patterns not shown). The reasonably good agreement between their XRPD diffractograms and FTIR spectra suggests that these two forms have very similar crystal structures. This circumstance is observed on an obligatory basis if the racemate consists of homochiral crystals, representing an eutecticum of its enantiomers and defined as a racemic conglomerate. However, the melting point of the eutecticum (i.e., a conglomerate) has to lie distinctively lower, in contrast to those of involved pure substances (i.e., the enantiomers). Felodipine enantiomer (En-mod. I) and racemate (mod. I) show essentially the same melting range. As a result, the similar crystal structures are explained by the existence of a solid solution. In this case, a single, homogeneous, crystalline phase is formed by mixtures of the two enantiomers in any proportion, whereby the equimolecular composition is termed a pseudoracemate or racemic solid solution.

Binary Phase Diagram

To evaluate the curve course of the solid solutions between (+)- and (−)-felodipine (En-mod. I), mixtures of racemic mod.I and (+)-En-mod. I were investigated by hot-stage microscopy and DSC. To avoid thermal decomposition, crystals of different compositions were crystallized from solvent (2-propanol/*n*-hexane, 27:20). The DSC traces of mod. I and (+)-En-mod. I and their quantitative mixtures are compiled in Figure 6a. These traces show respective endothermic melting peaks of single phases. The peak values were used to schematically mark the curve course in the phase diagram (Fig. 6b) relating the composition to the melting point, and the width of the DSC peaks served to estimate the temperature

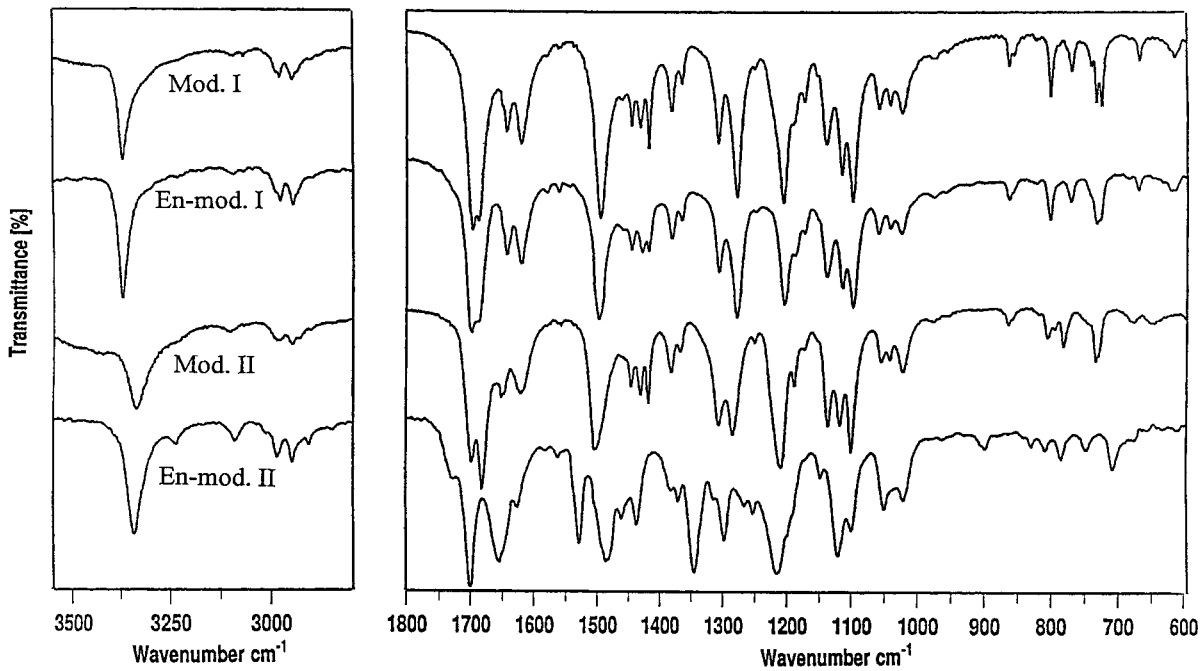

Figure 5. FTIR spectra of (±)-felodipine mod. I, II, and (+)-felodipine En-mod. I and II.

range between solid and liquid. The obtained measurements are relatively imprecise because the true liquid/solid equilibria are practically impossible to establish in the case of solid solutions,[17] especially if an additional decomposition broadens the melting peak. But it is obvious in Figures 6a and 6b that the system shows no eutectic melting in the whole range. This result establishes a continuous series of mixed crystals, which was also proved by "isomorphous growth" in the Kofler's contact method.[18]

The melting points of the unstable modifications of racemic and enantiomeric felodipine (mod. II and En-mod. II) are also marked in the phase diagram. Their curve course in the binary system could not be determined because of their instability. However, the strongly differing FTIR spectra of mod. II and En-mod. II (Fig. 5) clearly indicate *no* isomorphic relationship between them. Therefore, the formation of an additional continuous series of mixed crystals (isodimorphism) can be *excluded*.

DISCUSSION

We conclude, on the basis of the results just presented, that racemic felodipine may exist in two polymorphic, monotropically related crystal forms (mod. I and II) as well as in an acetone solvate (S_{Ac}). The partial thermal decomposition of racemic felodipine at melting temperatures led to slightly differing melting point specifications and to the assumption, in the literature,[2]of further modifications.

Mod. I shows a higher melting point as well as a higher enthalpy of fusion than mod.II (Table 1). By application of the heat-of-fusion rule,[19] mod. I represents the thermodynamically stable crystal form in the whole temperature range, which is referred to as monotropism. Although mod. II is an unstable form, it shows a significant kinetic stability. However, an application of mod. II as raw material in pharmaceutical processes is not advisable because of its poorly reproducible crystallization.

The acetone solvate S_{Ac} readily transforms into mod.I within a few days at ambient conditions. Because of the content of an organic solvent in its crystal structure combined with its instability, S_{Ac} cannot be used in pharmaceutical materials. On the other hand, the controlled and complete transformation of S_{Ac} leads to the well-defined crystal form of the thermodynamically stable mod. I. As Morris et al. emphasized in 1998,[20] factors such as particle shape, size, or surface characteristics have to be considered in attempts to improve specifications of raw materials and their processing. An optimization of tableting and dissolution behavior may be expected because of a

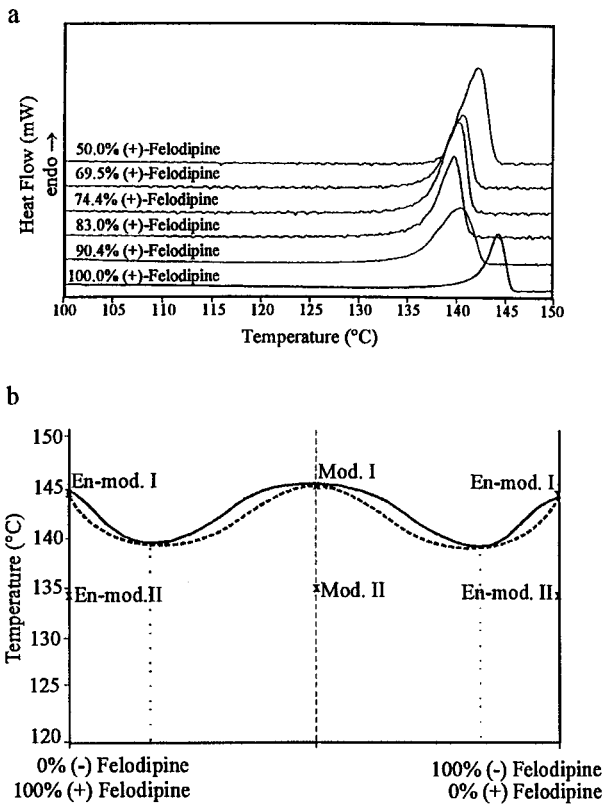

Figure 6. (**a**) DSC traces of (±)-felodipine mod. I, (+)-felodipine En-mod. I, and their quantitative mixtures crystallized from 2-propanol/*n*-hexane (27:20).(**b**) Binary melting phase diagram of (+)- and (−)-felodipine with the schematic liquid (─) and solid (-) curve course of the continuous series of mixed crystals.

dramatic increase in surface area of mod. I gained by desolvation from S_{Ac} as opposed to mod. I crystallized from solvents.

The melting phase diagram indicates a continuous series of mixed crystals in the binary system of felodipine enantiomers. Although this phenomenon is relatively rarely observed,[17,21,22] there are still some examples of solid solutions between enantiomers of rather well-known drug substances; for examples, hyoscyamine (atropine),[23] pindolol,[24] or atenolol.[25] Isomorphism between the two higher melting and thermodynamically stable crystal forms of (+)- and (−)-felodipine is indicated by a lack of an eutectic melting and the similarities in FTIR spectra and XRPD patterns. As recently demonstrated by Li and co-workers,[22] the identification of the racemic species (racemic compound, conglomerate, or pseudoracemate) is strongly suggested by thermodynamic calculation. Knowledge of the racemic species represents a basic requirement for choosing the resolution technique that will result in successful separation of opposite enantiomers. However, the thermodynamic parameters show less evidence for differentiation between a conglomerate and a pseudoracemate. Thus, a solid thermoanalysis is absolutely necessary for determining the racemic species.

Of high interest is the unusual shape of solid solutions in the binary system of felodipine enantiomers (En-mod. I). As seen in Figure 6b, the curve passes through a maximum in the racemic mixture and is flanked by two minima at ~20 and 80% (+)-felodipine. In 1899, Roozeboom[26] characterized three types of continuous solid solutions: Type I with an ideal curve course, type II with maximum melting and a nonideal curve course, and type III with minimum melting and a nonideal curve course. Roozeboom's classification of continuous series of mixed crystals does not provide for the curve course presented here. Looked at more closely, it represents a combination of types II and III, which was characterized by Brandstätter-Kuhnert and Aepkers in 1962 and termed as type II b.[27] Two examples forming this unusual shape are known in literature: the binary system of ethyl(1-methyl butyl)-barbituric acid and ethyl propyl-barbituric acid (mod. II),[28] and the binary system of (+)- and (−)-7,8-dihydro kawain characterized by a crossed isodimorphism.[29] Both of these curve courses exist for the most part in an unstable phase. Therefore, it is the first time that this series of solid solutions, established in the binary system of felodipine enantiomers, could be identified in a thermodynamically stable phase for any mixture.

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REFERENCES

1. Mannhold R. 1995. Calciumantagonisten vom Dihydropyridintyp: Medizinisch—chemische und

molekularpharmakologische Eigenschaften. Pharm i u Zeit 24:137–153.
2. Srčič S, Kerč J, Urleb U, Zupančič I, Lahajnar G, Kofler B, Šmid-Kobar J. 1992. Investigation of felodipine polymorphism and its glassy state. Int J Pharm 87:1–10.
3. Burger A, Koller KT. 1996. Polymorphism and pseudopolymorphism of nifedipine. Sci Pharm 64:293–301.
4. Grunenberg A, Keil B, Henck J-O. 1995. Polymorphism in binary mixtures, as exemplified by nimodipine. Int J Pharm 118:11–21.
5. Kuhnert-Brandstätter M, Völlenklee R. 1986. Beitrag zur Polymorphie von Arzneistoffen 2. Mitteilung: Halofenat, Lorcainidhydrochlorid, Minoxidil, Modipamol und Nitrendipin. Sci Pharm 54:71–82.
6. Burger A, Rollinger JM, Brüggeller P. 1997. Binary system of (R)- and (S)-nitrendipine - Polymorphism and structure. J Pharm Sci 86:674–679.
7. Henck J-O, Griesser UJ, Burger A. 1997. Polymorphie pharmazeutischer Wirkstoffe. Eine wirtschaftliche Herausforderung ? Pharm Ind 59:165–169.
8. Byrn S, Pfeiffer R, Ganey M, Hoiberg C, Poochikian G. 1995. Pharmaceutical solids: A strategic approach to regulatory considerations. Pharm Res 12:945–954.
9. Berntsson P, Carter RE. 1981. Determination of the conformation of felodipine by 1H NMR spin-lattice relaxation time measurements. Acta Pharm Suec 18:221–226.
10. Alajarin R, Jordan P, Vaquero JJ, Alvarez-Builla J. 1995. Synthesis of unsymmetrically substituted 1,4-dihydropyridines and analogous calcium antagonists by microwave heating. Synthesis 4:389–391.
11. Yiu S, Knaus EE. 1996. An improved synthesis of high purity felodipine. Org Prep Proceed Int 28:91–96.
12. Lamm B, Simonson R. 1989. Synthesis of the enantiomers of felodipine and determination of their absolute configuration. Tetrahedron Lett 30: 6423–6426.
13. Soons PA, Cohen AF, Breimer DD. 1993. Comparative effects of felodipine, nitrendipine and nifedipine in healthy subjects: Concentration-effect relationships of racemic drugs and enantiomers. Eur J Clin Pharmacol 44:113–120.
14. Kraus W, Nolze G. 1997. PowderCell for windows (V 1.0). Program for manipulation of crystal structures and calculation of X-ray powder patterns. Berlin, Germany: Federal Institute for Materials Research and Testing.
15. Fossheim R. 1986. Crystal structure of the dihydropyridine Ca-antagonist felodipine. Dihydropyridine binding prerequisites assessed from crystallographic data. J Med Chem 29:305–307.
16. Bar I, Bernstein J. 1985. Conformational polymorphism VI: The crystal and molecular structures of form II, III and V of 4-amino-N-2-pyridinylbenzenesulfonamide (sulfapyridine). J Pharm Sci 74:255–263.
17. Jacques J, Collet A, Wilen SH. 1981. Enantiomers, racemates and resolutions New York: J. Wiley and Sons.
18. Kofler L, Kofler A, Brandstätter M. 1954. Thermomikromethoden zur Kennzeichnung organischer Stoffe und Stoffgemische. Weinheim: Verlag Chemie.
19. Burger A, Ramberger R. 1979. On the polymorphism of pharmaceuticals and other molecular crystals. I: Theory of thermodynamic rules. Mikrochim Acta II:259–271.
20. Morris KR, Nail SL, Peck GE, Byrn SR, Griesser UJ, Stowell JG, Hwang S-J, Park K. 1998. Advances in pharmaceutical materials and processing. PSTT 1:235–245.
21. Eliel EL, Wilen SH, Mander LN. 1994. Stereochemistry of organic compounds. New York: J. Wiley and Sons, Inc.
22. Li ZJ, Zell MT, Munson EJ, Grant DJW. 1999. Characterization of racemic species of chiral drugs using thermal analysis, thermodynamic calculation, and structural studies. J Pharm Sci 88:337–346.
23. Kuhnert-Brandstätter M, Linder R. 1976. Beitrag zur thermischen Analyse und zur Polymorphie optischer Antipoden: L-Hyoscyamin — Atropin. Mikrochim Acta I:513–520.
24. Neau SH, Shinwari MK, Hellmuth EW. 1993. Melting point phase diagrams of free base and hydrochloride salts of bevantolol, pindolol and propanolol. Int J Pharm 99:303–310.
25. Burger A, Rollinger JM, Lindner W. 1999. Fundamentals and predictions of resolution of enantiomer mixtures by crystallization in the example of phase diagrams of atenolol and atenolol hydrochloride salt. Pharmazie 54:47–51.
26. Roozeboom HWB. 1899. Löslichkeit und Schmelzpunkt als Kriterien für racemische Verbindungen, pseudoracemische Mischkrystalle und inaktive Konglomerate. Z Phys Chem 28:494–517.
27. Brandstätter-Kuhnert M, Aepkers M. 1962. Molekülverbindungen, Mischkristallbildung und neue Polymorphiefälle bei Barbituraten. I. Mitt. Mikrochim. Acta 1041–1054.
28. Brandstätter M. 1942. Isomorphie und Polymorphie bei Barbitursäurederivaten. Z Phys Chem 191:227–240.
29. Kuhnert-Brandstätter M, Langhammer L. 1968. Binäre Systeme von enantiomeren Kawa-Laktonen. Arch d Pharm 301:351–356.