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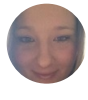

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Crystallization and Polymorphism of Felodipine

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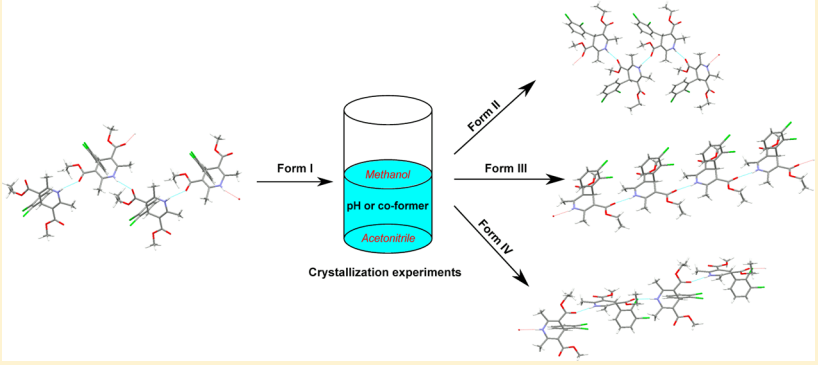

ABSTRACT: Two previously known polymorphs (forms I and II) and two new polymorphs (forms III and IV) of the calcium-channel blocker felodipine were obtained during attempts to cocrystallize the compound with a variety of potential cocrystal formers. A correlation was observed between the polymorphic outcome and the effective pH value in the presence of the cocrystal former, and it was possible subsequently to produce the four polymorphs by pH adjustment using H_2SO_4(aq) or NaOH(aq). This suggests that there is no distinct "structure-directing" role for the molecular additives present during the cocrystallization trials. The crystal structures of the new forms III and IV were determined using single-crystal X-ray diffraction. Forms I, II, and III were obtained in bulk form and characterized by a variety of analytical methods, including thermal analysis, solution calorimetry, intrinsic dissolution rate measurement, and solubility measurement. Form IV could be obtained only as a few isolated single crystals, and its crystallization could not be reproduced. On the basis of the measured thermochemical data and solubility studies, form I appears to be the thermodynamically most stable phase at ambient conditions, although the new form III is practically isoenergetic. Form II shows the highest solubility and intrinsic dissolution rate, consistent with the lowest thermodynamic stability. Forms I, II, and III are all monotropically related.

1. INTRODUCTION

Different polymorphs of a given crystalline drug substance can have different physicochemical properties, such as melting temperature, solubility, stability, dissolution rate, and bioavailability,[1] which may affect their usefulness in drug formulations. Systematic screening for polymorphs has therefore become an essential step in drug development to select as far as possible optimal properties for the drug particles and to avoid problems caused by polymorphic transitions during processing.[2] It is known that the crystallization of polymorphs can be affected by numerous factors, for example, the nature of solvents[3] and the presence of polymers[4] or other additives.[5] However, the mechanisms that lead to crystallization of different polymorphs remain poorly understood, and crystallization protocols, therefore, remain widely empirical. In spite of the relevance of polymorphism for drug substances, and for molecular crystals in general, the phenomenon remains largely unpredictable.

This paper focuses on the well-known drug felodipine (systematic name: ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate) (Figure 1). The compound is a calcium-channel blocking agent, widely

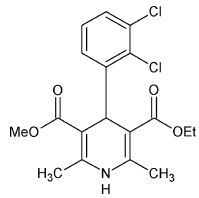

Figure 1. Chemical structure of felodipine.

used for treatment of hypertension and prevention of angina.[6] According to the Biopharmaceutical Classification Scheme (BCS),[7] felodipine belongs to Class II; that is, it is practically

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Table 1.

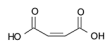
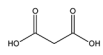
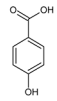
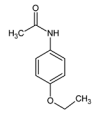
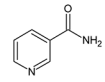
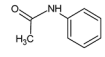
Co-former	pK_a value [a]	structure of additive	mole ratio	solvent	result
none				methanol, acetonitrile, ethanol	form I
maleic acid	pK_{a1} 1.83 pK_{a2} 6.07		1:1, 2:1	methanol	form II
			1:1, 2:1	acetonitrile	form III
			1:1	2-propanol	form III
			1:1	ethanol	form I
oxalic acid	pK_{a1} 1.23 pK_{a2} 4.19		1:1, 2:1	methanol,	form II, form IV (only once)
			1:1, 2:1	acetonitrile	form II
malonic acid	pK_{a1} 2.83 pK_{a2} 5.69		1:1	methanol, acetonitrile, ethanol	form II
succinic acid	pK_{a1} 4.16 pK_{a2} 5.61		1:1	methanol, acetonitrile, ethanol	form II
DL-malic acid	pK_{a1} 3.40 pK_{a2} 5.11		1:1	methanol, acetonitrile, ethanol	form II
tartaric acid	pK_{a1} 2.98 pK_{a2} 4.34		1:1	methanol, acetonitrile	form II
			1:1	ethanol	form I
acetamide	pK_a 15.1		1:1	methanol, acetonitrile	form II
			1:1	ethanol	form I
4-hydroxybenzoic acid	pK_{a1} 4.48 pK_{a2} 9.39		1:1	methanol	form II
			1:1	acetonitrile	form III
phenacetin	pK_a 2.20		1:1	methanol,	form II
			1:1	acetonitrile	form III
isonicotinamide	pK_a 10.61		1:1	methanol, acetonitrile	form II
nicotinamide	pK_a 3.30		1:1	methanol	form I
salicylamide	pK_a 8.31		1:1	methanol, acetonitrile	form II
pyrazinamide	pK_a 0.50		1:1	methanol	form II
			1:1	acetonitrile	form I
isoniazid	pK_{a1} 1.80 pK_{a2} 3.50		1:1	methanol	form II
			1:1	acetonitrile	form I
acetanilide	pK_a 0.50		1:1	methanol, acetonitrile	form I

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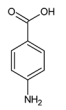
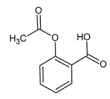
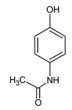
Table 1. continued

Co-former	pK_a value[a]	structure of additive	mole ratio	solvent	result
4-aminobenzoic acid	pK_{a1} 2.46 pK_{a2} 4.62		1:1	methanol, acetonitrile	form I
acetylsalicylic acid	pK_a 3.50		1:1	methanol, acetonitrile	form I
paracetamol	pK_a 9.63		1:1	methanol, acetonitrile	form I

[a]Literature sources for pK_a values: refs 16−18.

insoluble in water but has good permeability and is completely absorbed from the gastrointestinal tract.[8] Two polymorphs of felodipine are currently well established in the literature. Form I, used in marketed products, is the most stable one, and it crystallizes from methanol, ethanol, acetonitrile, and other common solvents. Its crystal structure was determined in 1986.[9] Form II was first mentioned in 1992 in a paper by Srčič et al.[10] However, no details were given for preparation of the polymorph, and a single-crystal X-ray structure was not determined. Polymorphism of racemic and enantiomeric felodipine was carefully studied in 2001 by Rollinger and Burger.[11] Their procedure for obtaining form II lacked reproducibility, however, and they were also not able to obtain any crystal structure. Although they found form II to be relatively stable, they did not recommend its use due to poor crystallization behavior. Single crystals of form II suitable for determination of its crystal structure were finally prepared by Lou *et al.*[12] during an attempt to cocrystallize felodipine with isonicotinamide in methanol. This led to the suggestion that isonicotinamide plays an important structure-directing role in the formation of the metastable felodipine polymorph II. In contrast to Rollinger and Burger,[11] who found forms I and II to be monotropically related, Lou *et al.*[12] reported an enantiotropic relationship. In the present paper, we set out to confirm the thermodynamic relationship between the established forms I and II and to study the potential structure-directing role of cocrystal formers on the crystallization of felodipine. We also had in mind the potential existence of a third polymorph, which was mentioned in the literature 20 years ago.[10]

2. MATERIALS AND METHODS

2.1. Compounds and Solvents. Felodipine ($C_{18}H_{19}Cl_2NO_4$, MW 384.25, 99.8%) was generously donated by Everlight (Everlight Chemical Industrial Corporation, Taipei, Taiwan 106). The bulk sample was received as crystalline form I. All cocrystal formers and solvents were purchased from Sigma-Aldrich (Denmark). All starting materials, including felodipine, were used without purification for the crystallization experiments.

2.2. Crystallization. In 2 mL of the respective solvents or mixtures of solvents, 50 mg of felodipine was dissolved, together with molar ratios of the intended cocrystal formers (Table 1, and allowed to evaporate in the fume cupboard. For pH controlled crystallization, felodipine (50 mg) was dissolved in 10.0, 8.0, 6.0, 4.0, and 2.0 mL of acetonitrile or methanol, respectively. To each sample, 0.5 mL of an aqueous solution of known pH (pH = −0.8, 1.0, 3.0, 4.0, 9.0, 10.0, 11.0, or 13.0) was added. pH values were adjusted using H_2SO_4(aq) or NaOH(aq). A "blind" experiment in 0.5 mL of distilled water (pH = 6.0) was also carried out. All crystalline products were identified by X-ray powder diffraction (XRPD).

2.3. X-ray Diffraction Methods. Single-crystal X-ray diffraction data were collected on a Bruker-Nonius X8-APEXII CCD diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.7107 Å) at 150 K. X-ray powder diffraction data were recorded at ambient conditions in Bragg−Brentano geometry with either a Siemens D5000 instrument using monochromated Cu Kα_1 radiation (λ = 1.5406 Å) or a PANalytical X'Pert Pro diffractometer with a PIXcel detector and nonmonochromated Cu Kα radiation (λ = 1.5418 Å).

2.4. Solid-State Milling. Solid samples were milled using a Retsch MM400 ball mill, using 25 mL stainless steel containers with one stainless steel ball (Ø 15 mm), shaken at 17.5 Hz for 20 min. The ground solids were analyzed immediately by XRPD.

2.5. Solubility Determination. Solubility experiments were carried out by the shake-flask method. Suspensions of the respective polymorphs in 15 mL of a 50% ethanol−water mixture in plastic vials were shaken in a water bath (Julabo SW23 from Julabo Labortechnik GmbH, Seelbach, Germany) for 3 days at 25 ± 0.1 °C. The solid phase was removed by filtration (VWR syringe filter, PTFE, 0.45 μm). The molar solubilities were measured spectrophotometrically with an accuracy of 2−2.5% using a protocol described previously[13] using a UV−vis spectrophotometer (Genesys 10UV-Scanning, Thermo Fisher Scientific, USA) at the reference wavelength (238 nm). The results are expressed as the average of at least three independent experiments. XRPD of the bottom phase was used to monitor possible polymorphic conversions, but none were found to occur.

2.6. Intrinsic Dissolution Rate Measurements. The method is described in European Pharmacopoeia 7.0.[14] 200 mg of the respective polymorph of felodipine was compressed with a hydraulic press for 3 min to form a nonporous compact of 8 mm diameter. The holder of the Pharma Test PTWS 310 apparatus (PharmaTest Apparatebau GmbH, Hainburg, Germany) with this sample was rotated at 100 rpm in 300 mL of 50% ethanol−water mixture at 25.0 ± 0.5 °C. The cumulative amount dissolved per unit surface area was determined by taking aliquots of 3 mL of the respective media every 5−6 min with volume replacement and concentration measured in a UV−vis

Table 2. Selected Crystallographic Data for Felodipine Polymorphs I–IV

	Form I[9]	Form II[12]	Form III	Form IV
empirical formula	$C_{18}H_{19}Cl_2NO_4$	$C_{18}H_{19}Cl_2NO_4$	$C_{18}H_{19}Cl_2NO_4$	$C_{18}H_{19}Cl_2NO_4$
formula weight	384.24	384.24	384.24	384.24
T (K)	123	150	150	150
crystal system	monoclinic	monoclinic	monoclinic	monoclinic
space group	$P2_1/c$	$C2/c$	$P2_1/n$	$P2_1/n$
a (Å)	12.086(3)	32.392(7)	15.1255(18)	11.1129(9)
b (Å)	12.077(2)	18.717(4)	7.2302(9)	12.5688(11)
c (Å)	13.425(2)	23.771(5)	17.2796(19)	13.4969(11)
α (deg)	90	90	90	90
β (deg)	116.13(1)	91.00(3)	110.198(7)	107.009(4)
γ (deg)	90	90	90	90
volume (Å^3)	1759.3(1)	14373(5)	1773.5(4)	1802.7(3)
Z/Z'	4/1	32/4	4/1	4/1
calcd density (mg/m^3)	1.451	1.421	1.439	1.416
absorption coeff (mm^{-1})	0.390	0.338	0.389	0.383
crystal size (mm)			0.46 × 0.18 × 0.08	0.20 × 0.18 × 0.08
data collected			25925	25633
unique data			3145	3180
R_{int}			0.065	0.095
obsd data [$I > 2\sigma(I)$]			2276	1992
$R1$ [$I > 2\sigma(I)$]			0.063	0.076
$wR2$ (all data)			0.144	0.198
goodness-of-fit (on F^2)			1.12	1.03
diff. density (e·Å^{-3})			−0.44, 0.58	−0.63, 0.60
CCDC	DONTIJ	DONTIJ01	864026	864027

spectrophotometer (Genesys 10UV-Scanning, Thermo Fisher Scientific, USA) at the reference wavelength (238 nm). Concentrations were calculated according to an established calibration curve. Triplicate analyses were performed for each polymorph. The slope of the plot of mass dissolved per unit surface area vs time gives the intrinsic dissolution rate in appropriate units, e.g. mg·min^{-1}·cm^{-2}. Conversion of the polymorphs during dissolution studies was excluded using XRPD.

2.7. Solution Calorimetry. Enthalpies of dissolution (ΔH^m_{sol}) were measured using a Precision Solution Calorimeter in the 2277 Thermal Activity Monitor (both from Thermometric AB, Järfälla, Sweden). The software SolCal version 1.2 (Thermometric) was applied for all calculations. The measuring temperature was 25.0 ± 10^{-4} °C, the volume of the vessel was 100 mL, the solvent was ethanol, the stirrer speed was 400 rpm, and the mass of the sample was approximately 65 mg, measured with an accuracy of ±0.05 mg. The number of samples measured for each of the respective phases was not less than five, depending on the reproducibility of the results. The calorimeter was calibrated using KCl (analytical grade >99.5%, from Merck) in water over a wide concentration interval (sample masses between 18 and 100 mg) with more than 10 measurements. The standard value of solution enthalpy obtained was ΔH^m_{sol} = 17225 ± 50 J·mol^{-1}. This is in good agreement with the value recommended by IUPAC of ΔH^m_{sol} = 17217 ± 33 J·mol^{-1}.[15]

2.8. Differential Scanning Calorimetry (DSC). Thermal analysis was carried out using a DSC 204 F1 Phoenix differential scanning heat flux calorimeter (NETZSCH, Germany) with a high sensitivity μ-sensor. The sample was heated at the rate 10 K·min^{-1} in an argon atmosphere and cooled with gaseous nitrogen. The temperature calibration of the DSC instrument was performed against six high-purity substances: cyclohexane (99.96%), mercury (99.99+%), biphenyl (99.5%), indium (99.999%), tin (99.999%), and bismuth (99.9995%). The accuracy of the weighing procedure was ±0.01 mg.

3. RESULTS AND DISCUSSION

3.1. Crystallization Experiments. Cocrystallization experiments were set up for felodipine with 18 structurally varied cocrystal formers in 1:1, 1:2, and 2:1 molar ratios. The choice of solvents was restricted by the solubilities of felodipine and the coformers in methanol, acetonitrile, and ethanol. An overview of the crystallization experiments is given in Table 1. As has been reported in similar attempts,[12] the present cocrystallization attempts resulted in the formation of polymorphs of felodipine, rather than any cocrystals. The known polymorphs, forms I and II, were produced, plus two new polymorphs, referred to as forms III and IV.

Form II crystallized from methanol in the presence of several cocrystal formers (Table 1). Previously, Lou *et al.*[12] claimed that isonicotinamide acted as a specific additive to induce crystallization of form II. The present results demonstrate that the same polymorph can be obtained also in the presence of several structurally diverse additives. From acetonitrile in the presence of three different molecules, namely maleic acid, phenacetin, and 4-hydroxybenzoic acid, the new form III crystallizes. If the solvent is methanol instead of acetonitrile, the same mixtures generate form II. Again, the formation of a specific polymorph cannot be explained therefore by the specific presence of these additives. Form IV of felodipine was obtained only in one single instance and under the same conditions as those for form II. Crystals of form IV were subsequently used to seed solutions of felodipine (without coformers) in methanol and acetonitrile, respectively, but in all cases this resulted in mixtures of form III and form IV. Thus, we were not able to produce bulk samples of form IV in a controlled manner. Given the structural diversity of the additives that provide similar

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crystallization outcomes, it is plausible that the polymorphism is not directly related to any structural feature of the additive, but rather to another property of the crystallization medium. Since all of the additives are carboxylic acids or amides, pH is a likely source.

3.2. pH-Controlled Crystallizations. Considering the pK_a values of the cocrystal formers listed in Table 1, it appears that form II crystallizes with more basic additives, while forms II and III crystallize with more acidic additives. To test this hypothesis, felodipine (50 mg) was dissolved in 10, 8, 6, 4, or 2 mL of acetonitrile or methanol. To each sample, 0.5 mL of water was added with a certain pH adjusted by addition of either H_2SO_4(aq) or NaOH(aq). A control test with addition of 0.5 mL of distilled water (pH 6.0) produced only form I. In methanol, form III was produced exclusively at pH 1.0, while form II was produced exclusively at pH 3. To either side of these values (pH −0.8 and 4), mixtures of forms II and III were observed. In acetonitrile, form III was produced exclusively at pH 3 and 4, while pH 1 and −0.8 produced mixtures with form I or in some cases no crystalline product. In methanol at pH 13, form II was observed in all samples, frequently also with forms I and III. The smallest volumes of MeOH (2.5 mL) produced only form II for all of the basic solutions (pH 9, 10, 11, 13). The results from acetonitrile under basic conditions were less clear, producing mixtures of forms I, II, and III. Form IV was produced during the pH tests only twice, at pH 13 with 4 or 6 mL of MeOH, and in both cases as a mixture with form II. The reproducibility of the results was considered by making duplicate trials for several points in the matrix (see Tables S1A and S1B in the Supporting Information). In general, the reproducibility did not contradict the trends, but a given condition did not always provide an equivalent result. It is possible that the system is sensitive to seeding, and accidental nucleation may occur due to the blending procedure of the felodipine solution with the water.

3.3. Polymorph Transformations. The tendency for transformation between the polymorphs was examined by slurrying experiments and in the solid state by mechanical milling. For samples of the individual polymorphs slurried in water, acetonitrile, or methanol solutions at ambient conditions, form II transforms to form I after several days, while forms I and III remain stable in all solvents. Addition of acid or base did not affect these results. For a 1:1 mixture of forms I and III in methanol, however, only form I was present after several days, establishing form I to be thermodynamically most stable under these conditions. During solid-state milling, form II transformed to form I, while forms I and III remained unchanged.

3.4. Crystal Structures. A summary of the crystallographic data is given in Table 2. In all four polymorphs, the molecular conformation is comparable, comprising two essentially planar units with the plane of the dichlorophenyl group perpendicular to the plane of the remainder of the molecule. The pyridyl ring in form III is distorted more significantly from planarity compared to the other structures.

The orientation of the methyl and ethyl ester groups is such that the carbonyl O atom points toward the methyl groups either side of the pyridyl N atom in forms I and II, while the ethyl ester adopts the opposite orientation in forms III and IV (visible in Figure 2). In our refinement of form III, some disorder is apparent in the positions of the methyl and ethyl ester groups, in a refined ratio 0.837(11):0.163(11). Interchange of the methyl and ethyl chains in this way serves formally to invert the chirality of the felodipine molecule. Disorder of this type is not observed in any of the other structures (although the published structure of form II contains some positional disorder of the ethyl groups in one crystallographically distinct molecule).

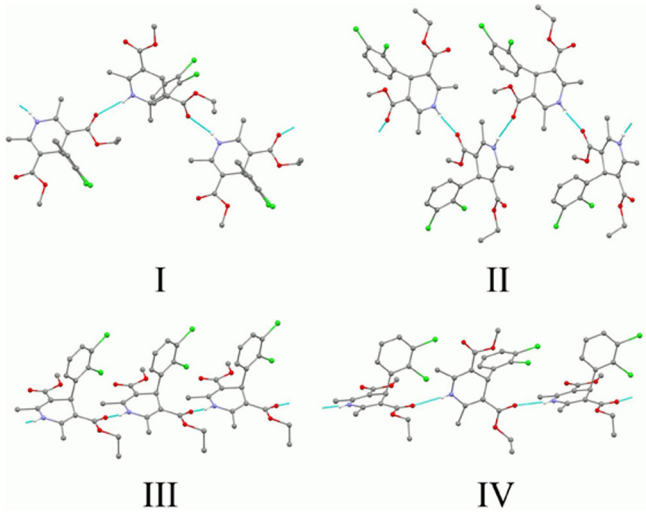

Figure 2. Hydrogen-bonding motifs in polymorphs I–IV.

All four structures contain N–H···O hydrogen bonds from the pyridyl N atom to the carboxyl O atoms of the methyl/ethyl ester groups (Table 3). In forms III and IV, these define distinct linear ribbons (Figure 2). In III, all molecules in the ribbon are related by crystallographic translation (along *b*), while, in IV, adjacent molecules (related by the *n*-glides) are turned so that their pyridyl planes lie approximately perpendicular to each other. The ribbons in form III comprise exclusively molecules of one enantiomer, while those in form IV contain molecules of opposite chirality alternating along a given chain. The minor disorder of the methyl and ethyl esters apparent in form III could represent some disruption of the homochiral nature of individual ribbons, or it could reflect disorder of adjacent homochiral ribbons. In forms I and II, the hydrogen bonds define "zig-zag" arrangements, with form I containing bifurcated N–H···O interactions.

Table 3. Intermolecular Hydrogen Bonds in Polymorphs I–IV

	D–H···A	D–H/Å	H···A/Å	D···A/Å	D–H···A/deg
	Form I[9]				
a	N1–H1···O3[a]	0.833	2.433	3.238(3)	163(3)
b	N1–H1···O1[b]	0.833	2.674	3.155(4)	119(3)
	Form II				
a	N1–H1···O6	0.879	2.019	2.887(5)	168.9(3)
b	N2–H2···O9	0.879	2.107	2.950(5)	160.6(3)
c	N3–H3···O13	0.881	2.033	2.899(5)	167.3(3)
d	N4–H4···O1[c]	0.881	2.082	2.931(5)	161.7(3)
	Form III				
a	N1–H1···O1[d]	0.802	2.195	2.9603(3)	159.65(3)
	Form IV				
a	N1–H1···O1[e]	0.880	2.051	2.9300(2)	177.53(3)

[a]Symmetry code for acceptor atom: $(-x, {}^1/_2 + y, {}^1/_2 - z)$. [b]Symmetry code for acceptor atom: $(x, 1.5 - y, -{}^1/_2 + z)$. [c]Symmetry code for acceptor atom: $({}^1/_2 - x, {}^1/_2 - y, z)$. [d]Symmetry code for acceptor atom: $(x, 1 + y, z)$. [e]Symmetry code for acceptor atom: $({}^1/_2 + x, {}^1/_2 - y, {}^1/_2 + z)$.

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A recurring motif within the structures is a centrosymmetric "back-to-back" interaction between the pyridyl planes (Figure 3).

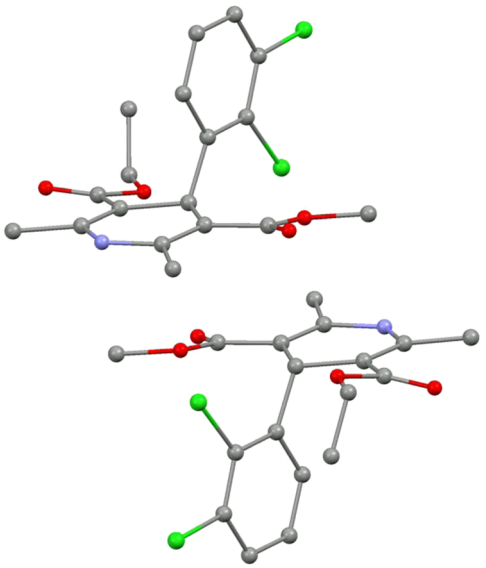


Figure 3. Centrosymmetric "back-to-back" arrangement present in all polymorphs.

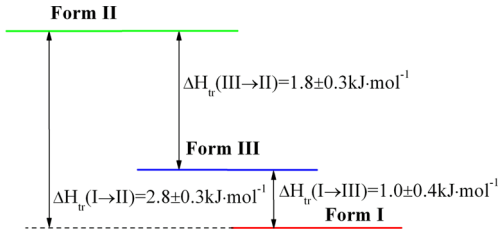
The interplanar distance is comparable in all four polymorphs (3.65−3.87 Å), but there are different degrees of lateral slip. The structures can be viewed as alternative packing arrangements of these centrosymmetric pairs.

In forms III and IV, the pairs are linked into linear ribbons by the N−H···O hydrogen bonds, and the polymorphism corresponds to turning every second dimer in each ribbon by *ca.* 90° in form IV compared to its orientation in form III. Form I can be viewed as stacks of molecular pairs (aligned along the *a* axis), with adjacent stacks turned 90° to each other. The interactions between molecular pairs within the stacks are face-to-face interactions between the dichlorophenyl groups, while the N−H···O hydrogen bonds link between stacks. The structure published for form II by Lou et al.[12] is interesting. It contains four crystallographically independent molecules, forming centrosymmetric pairs arranged into layers with local (noncrystallographic) translation symmetry. We have observed complex disorder within this structure, which will be described in detail elsewhere.

3.5. Solution Calorimetry. To establish thermodynamic relationships between the felodipine polymorphs, solution calorimetry experiments were carried out. We have used this approach previously to measure differences between other drug modifications.[20,21] In the present study, ethanol was chosen as the solvent, because felodipine dissolves well with a large endothermic heat effect. The results of the calorimetric experiments are summarized in Scheme 1 (see Table S2 of the Supporting Information for a full data set). Form I is most stable, although the differences compared to the other polymorphs are small: the crystal lattice energy of form III differs from that of form I by 1.0 ± 0.4 kJ·mol^{-1}, while form II is least stable, by 2.8 ± 0.3 kJ·mol^{-1} compared to form I. We were not able to measure the enthalpy of dissolution for form IV because of insufficient quantities.

3.6. Solubility and Intrinsic Dissolution Rate. Solubility and intrinsic dissolution rate measurements were performed in 50% ethanol−water mixtures to increase the solubility of felodipine sufficiently for the concentrations to be detectable

Scheme 1. Differences between Crystal Lattice Energies for the Felodipine Polymorphs, Established through Solution Calorimetry Measurements



by UV-spectrophotometry. It is well-known that the difference in free energy between polymorphs is directly proportional to their relative equilibrium solubilities[1] as expressed by the following equation:

$$\Delta G_{tr}^{T}(\mathrm{I} \rightarrow \mathrm{II}) = RT \ln\left(\frac{C_{II}}{C_{I}}\right) \quad (1)$$

where C_I and C_{II} are the solubilities of polymorphs I and II, respectively. On the other hand, intrinsic dissolution is a standardized kinetic method to exclude the effect of as many experimental variables as possible (e.g., particle size, stirring patterns, temperature, *etc.*), so it is better suited to compare polymorphs. The results of solubility and intrinsic dissolution studies are shown in Figure 4 and Table S3 (see Supporting Information). Table 4 shows ΔG from the solubility experiment, ΔH from solution calorimetry, and the calculated values of ΔS.

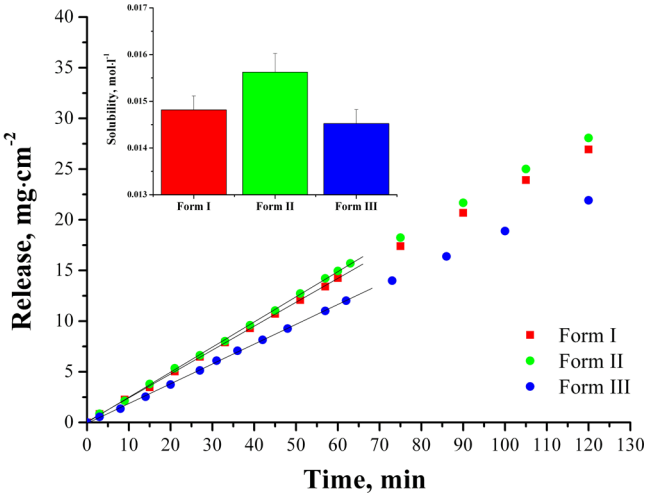


Figure 4. Intrinsic dissolution rates and solubilities of felodipine polymorphs in 50% ethanol solution. The results are expressed as mean ± SD, n = 3.

It was expected from the solution calorimetry experiments that form I should be most stable and least soluble. However, it was

Table 4. Thermodynamic Parameters of Polymorphic Transitions for Felodipine Forms from Solution Calorimetry and Solubility Experiments

polymorphic transition	ΔG_{tr}°, kJ·mol^{-1}	ΔH_{tr}°, kJ·mol^{-1}	ΔS_{tr}°, J·mol^{-1}·K^{-1}
form I → form II	0.131	2.8 ± 0.3	9.0
form I → form III	−0.050	1.0 ± 0.4	3.5
form III → form II	0.181	1.8 ± 0.3	5.4

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found that form III has essentially identical solubility (the measured difference between forms I and form III is not significant within the precision of the measurement technique). Form III shows the lowest intrinsic dissolution rate, while the intrinsic dissolution rate of form I is higher by a factor of 1.2 compared to form II. Both experiments indicate essentially the same rank order of stability for the polymorphs under the current conditions: form III most stable, closely followed by form I then form II. From the experimental data it is also possible to calculate the thermodynamic parameters for polymorphic transition between the different forms. The free energy of the polymorphic transition, ΔG°_{tr}, as calculated by eq 1, and enthalpy relationships from solution calorimetry enable estimation of the entropy contribution, ΔS°_{tr}, calculated by the following equation:

$$\Delta S^{T}_{tr}(I \rightarrow II) = \frac{\Delta H^{T}_{tr}(I \rightarrow II) - \Delta G^{T}_{tr}(I \rightarrow II)}{T} \quad (2)$$

The derived values of the thermodynamic parameters are summarized in Table 4. From the results it can be concluded that ΔS°_{tr} decreases in magnitude in the following order: form II > form III > form I.

3.7. DSC Experiments. DSC thermograms for forms I, II, and III are shown in Figure S1 (see Supporting Information), and the relevant data are listed in Table 5. There are no data for form IV due to insufficient amounts of material.

Table 5. Thermochemical Data for Felodipine Polymorphs

	form I	form II	form III
T_{fus}, °C (onset)	143.8 ± 0.2 (n = 2)	134.8 ± 0.2 (n = 2)	143.7 ± 0.2 (n = 4)
ΔH^{T}_{fus}, kJ·mol^{-1}	31.5 ± 0.5	27.6 ± 0.5	29.1 ± 0.5
ΔH^{298}_{fus}, kJ·mol^{-1}[a]	18.5	15.6	16.1
ΔS^{T}_{fus}, J·mol^{-1}·K^{-1}	75.9	67.1	71.5
ΔH^{298}_{tr}, kJ·mol^{-1} (DSC)	2.9 (→II)		0.5 (→II)
	2.4 (→III)		
T_{tr}, °C[b]		220.3 (→I)	145.4 (→I)

[a]Calculated according to the procedure proposed by Chickos and Acree.[23] [b]Calculated by eq 3.

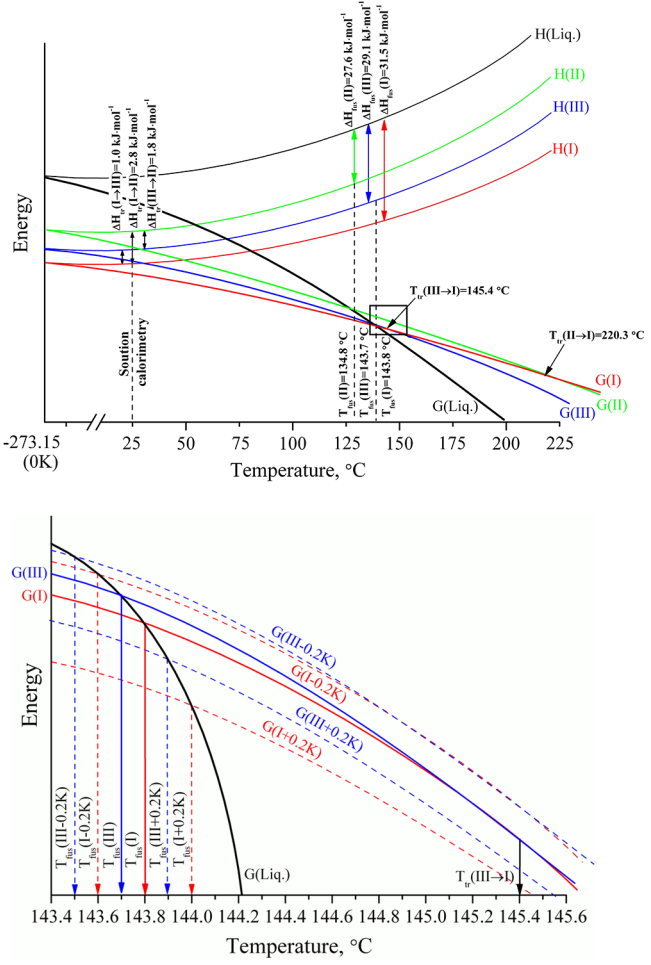
All polymorphs melt without other phase transitions. The melting temperatures and enthalpies of fusion of forms I and II are in good agreement with previously reported data.[11] The onset temperature of form III is identical to that of form I (within the precision of the measurement). The difference in heat of fusion between these two forms is also very small (2.4 kJ·mol^{-1}), showing again the essentially isoenergetic nature of these two polymorphs.

To study monotropy−enantiotropy relationships between the polymorphs, the thermodynamic transition temperature was calculated by the following equation based on equal free energies at the transition temperature between two polymorphs A and B:[21]

$$T_{tr}(A \rightarrow B) = \frac{(\Delta H^{T}_{fus}(A) - \Delta H^{T}_{fus}(B))}{\left(\frac{\Delta H^{T}_{fus}(A)}{T_{fus}(A)} - \frac{\Delta H^{T}_{fus}(B)}{T_{fus}(B)}\right)} \quad (3)$$

For enantiotropically related polymorphs, the calculated thermodynamic transition temperature T_{tr} is a real value below the lower melting point of the two polymorphs whereas in the case of a monotropically related pair this transition point is a virtual temperature above the melting points of the two crystal modifications. The calculated values for T_{tr} are given in Table 5. From the thermochemical results and thermodynamic transition temperatures, a schematic energy−temperature diagram (E−T diagram) according to Burger−Ramberger[22] has been constructed (Scheme 2).

Scheme 2. (top) Semischematic Energy vs Temperature Diagram for Felodipine Polymorphs Forms I and Form III. (bottom) Enlargement of the Area Indicated by the Rectangle in the Top of the Scheme (Dotted Lines Show Possible Gibbs Energy Trends Due to Estimated Experimental Errors)



The energy diagram shows that the temperature of transition of forms I and III is virtual (i.e., above the melting points of both polymorphs) even if the worst case scenario of experimental error is taken into account. In any case, a monotropic relationship is found. The thermodynamic stability of form I is supported by Burger−Ramberger's "density rule" (Table 2) as well as the solution calorimetry data (see above). The results also show clearly that the metastable form II is monotropically related to form I (Scheme 2). This statement is in agreement with Rollinger and Burger and in contrast to the conclusion of Lou *et al.*,[12] who claimed an enantiotropic relationship between the two forms. Apparently, during their slurry experiment, the transformation of form II to form I (which we also observed under similar conditions) passes through a dissolved state and is not suitable to study the transition between crystalline forms in terms of monotropy/enantiotropy.

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It is interesting to compare transition enthalpies between the different polymorphs derived from the solution calorimetry and the DSC experiments extrapolated to 298 K. To extrapolate DSC data to standard conditions, the procedure developed by Chickos and Acree[23] was applied (Table 5). The transition enthalpies obtained by DSC are rather high compared to the solution calorimetry results. However, both experiments suggest the energy arrangement of polymorphs in the same order: form I < form III < form II. The solubilities of forms I and III (Figure 4 and Supporting Information Table S3) coincide within experimental error, as do the calculated free energies. It should be noted that solubility studies involve significant experimental difficulties, e.g. connected to the separation of dissolved from nondissolved material and possible adsorption of molecules on surfaces, in addition to more common analytical errors. In other words, the solubility experiments also show that forms I and III are practically isoenergetic within the expected precision of those measurements. Similar examples of "isoenergetic polymorphs" have been described for other drug substances, e.g. cimetidine,[21] phenobarbital,[24] and paracetamol.[25]

Intrinsic dissolution rate measurements show a significant difference between forms I and III, and surprisingly, form I dissolves clearly faster than form III. Dissolution rates were measured directly in the UV spectrophotometer without dilution to avoid analytical errors as far as possible, and the error bars for three consecutive measurements are very small. Thus, these results should be most reliable. Any experiments where the polymorphs are in contact with a solvent may alter the outermost surface of the crystals, although this may not be readily detectable (e.g., by XRPD as in the present study), which may influence the dissolution rate on a molecular level. Therefore, solution calorimetry and DSC as bulk methods are more suitable to reveal thermodynamic stability relationships between polymorphs, but not dissolution kinetics. It is interesting to note that the significant difference in dissolution rate between forms I and III is in a different rank order than the thermodynamic stabilities revealed from solution calorimetry. Therefore, form I can clearly be regarded as optimum with respect to both its thermodynamic stability and its fast dissolution (in 50% EtOH).

4. CONCLUSIONS

Four polymorphs are now established for felodipine by single-crystal X-ray structures. Forms I–III have been thoroughly characterized in the bulk, while form IV has been obtained only as a few isolated single crystals. Form I is confirmed to be the thermodynamically most stable phase at ambient conditions, although the new form III is practically isoenergetic. Form II is less stable, possibly on account of increased entropy associated with disorder in the crystalline state. All of the polymorphs I–III are monotropically related. Like others, we first observed polymorphism for felodipine during attempted cocrystallization experiments. However, we find that the crystallization of the polymorphs can alternatively be realized by adjustment of the effective pH, which suggests that there is no distinct "structure-directing" role for the molecular additives present during the cocrystallization trials. Control over the polymorphic outcome during the pH based crystallizations is only partial. Although general trends are seen, isolated crystallization experiments can still produce different polymorphs in spite of apparently equivalent protocols. We have observed that the system is highly sensitive to seeding, and this provides our best explanation at the current time for some irreproducible crystallization results. The failure to produce form IV in a reliable way is possibly related to its instability to transformation during the crystallization protocols that we employed.

■ ASSOCIATED CONTENT

Supporting Information

Details relating to the pH-controlled crystallization experiments, solution calorimetry, intrinsic dissolution rate, solubility, powder X-ray diffractograms, and DSC thermograms; and crystallographic data for forms III and IV in CIF format (CCDC deposition numbers 864026 and 864027, respectively). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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