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Polymorphism of felodipine co-crystals with 4,4′-bipyridine

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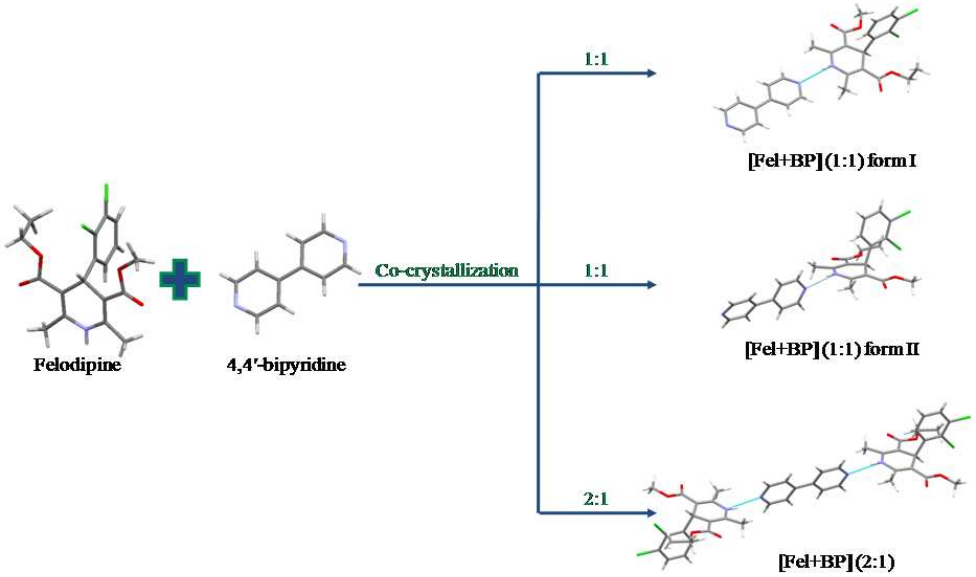
The calcium-channel blocking agent felodipine forms co-crystals with 4,4′-bipyridine with 1:1 and 2:1 molar ratios. The co-crystal with 1:1molar ratio exists in two polymorphic forms. The co-crystals were investigated by wide spectrum of experimental methods and approaches: X-ray diffraction, DSC, solution calorimetry and Hirshfeld Surfaces analysis. A survey of the CSD was performed to analyze the thermal stability of 4,4′-bipyridine co-crystals.



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Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

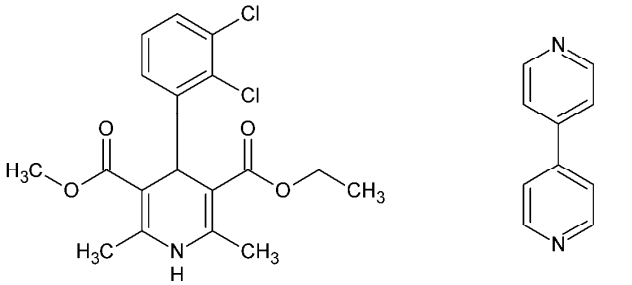
DOI: 10.1039/b000000x

The calcium-channel blocking agent felodipine (**Fel**) forms co-crystals with 4,4′-bipyridine (**BP**) with 1:1 and 2:1 molar ratios. The [**Fel+BP**] (1:1) co-crystal exists in two polymorphic forms. Differential scanning calorimetry and solution calorimetry show that form I of the [**Fel+BP**] (1:1) co-crystal is the thermodynamically most stable phase. The difference in the crystal lattice energies between different polymorphs of the co-crystal is found to be comparable with that for the polymorphic forms of pure felodipine. The enthalpies of formation of the co-crystals are small, which indicates that the packing energy gain originates from only weak van der Waals interactions. Analysis of Hirshfeld surfaces for the felodipine molecule shows a similar distribution of intermolecular contacts in the co-crystals and pure felodipine..

Introduction

In many cases, active pharmaceutical ingredients (API) can exist in different polymorphic forms, and polymorphism therefore plays a significant role in the pharmaceutical industry.[1] The phenomenon is highly undesirable during processing of drugs due to lack of predictability and, as a consequence, potentially uncontrollable changes of the physicochemical properties of a product. One potential way to address the polymorphism issue could be modification of the crystal structure of an API by formation of co-crystals (or salts, hydrates/solvates), since these have been postulated to show a lower propensity towards polymorphic behavior.[2] Although descriptions of co-crystal polymorphism have been relatively limited compared to single-component crystals, cases are now being reported quite regularly ,[3] and the early conclusion regarding their limited polymorphism seems likely to be a consequence of the relatively small data set that was available for statistical analysis at the time.[4] The majority of polymorphic co-crystals reported so far have shown only two polymorphs, but more cases of co-crystals with a greater number of polymorphs will probably emerge with time. For example, Ueto *et al.* have described five forms of the furosemide-nicotinamide (1:1) co-crystal.[5]

In this paper, we focus on the structures and physicochemical properties of three co-crystals of the API felodipine (**Fel**) with 4,4′-bipyridine (**BP**), namely two polymorphs of the co-crystal with a 1:1 molar ratio, and a co-crystal having a 2:1 molar ratio. This work is a continuation of our previous studies concerning new crystalline forms of felodipine.[6] Felodipine is one of the well-known calcium-channel blocking drugs,[7] and it is itself tetramorphic: forms I and II have been known for a long time,[8] and we have quite recently reported two new polymorphs, forms III and IV.[6a] Several solvates are also known in the literature. A solvate with formamide has been reported by Lou *et al.*,[9] and Rollinger and Burger have also described an unstable solvate with acetone, characterized by thermal, IR spectroscopic and powder X-ray diffraction techniques.[10] We have also reported felodipine solvates with the structurally-related high-boiling point solvents, dimethylacetamide, dimethylethyleneurea and tetramethylurea.[6b] To date, however, co-crystal formation for felodipine does not seem to have been systematically explored, and a hydrated co-crystal of felodipine with diazabicyclo[2.2.2]octane (DABCO) seems to be the only reported example.[6c] On the other hand, 4,4′-bipyridine is one of the most frequently chosen co-formers for co-crystallization trials. Co-crystals with 4,4′-bipyridine have been reported for a variety of well-known drugs, including paracetamol,[11] aspirin,[12] ibubrofen[12] and 4-aminobenzoic acid.[13] Polymorphism of co-crystals containing 4,4′-bipyridine has also been reported: for example, the pimelic acid-4,4′-bipyridine (1:1) co-crystal has three known polymorphs.[14]



Felodipine **4,4'-bipyridine**

Fig1 Molecular structures of felodipine and 4,4′-bipyridine

Materials and Methods

Compounds and solvents

Felodipine ($C_{18}H_{19}Cl_2NO_4$, MW 384.26, 99.8%) was generously gifted by Everlight (Everlight Chemical Industrial Corporation, Taipei, Taiwan 106) and presents polymorphic form I. All solvents and 4,4′-bipyridine were purchased from Sigma-Aldrich (Denmark). All of the starting materials, including felodipine, were used without further purification for the co-crystallization experiments.

Crystallization procedure

[Fel+BP] (1:1) form I. Equimolar amounts of felodipine and 4,4′-bipyridine were dissolved in acetone and stirred at room temperature. The resulting clear solution was filtered and allowed to evaporate. Diffraction quality crystals were grown over 2 days.

[Fel+BP] (1:1) form II. Equimolar amounts of felodipine and 4,4′-bipyridine were dissolved in methanol and stirred at room temperature. The resulting clear solution was filtered into a 2 ml test tube, covered by parafilm perforated with a few small holes, and allowed to evaporate slowly. Diffraction quality crystals were obtained over a week.

[Fel+BP] (2:1). Felodipine and 4,4′-bipyridine in a 2:1 molar ratio were dissolved in acetone and stirred at room temperature. The resulting clear solution was filtered into a 2 ml test tube, covered by parafilm perforated with a few small holes, and allowed to evaporate slowly. Diffraction quality crystals were grown over a few days.

For [Fel+BP] (1:1) form II and [Fel+BP] (2:1), the co-crystallization trials showed poor reproducibility**.**

Solvent-drop grinding

Solvent-drop grinding experiments were performed using a Fritsch planetary micro mill, model *Pulverisette* 7, in 12 ml agate grinding jars with ten 5 mm agate balls at a rate of 600 rpm for 60 min. The experiments were carried out with stoichiometric amounts of felodipine and 4,4′-bipyridine and a few drops of solvent (acetone, methanol or acetonitrile) added by micropipette.

X-ray diffraction

Single-crystal X-ray diffraction data were collected on a Bruker-Nonius X8-APEXII CCD diffractometer using graphite-monochromated MoKα radiation (λ = 0.7107 Å) at 150 K. X-ray powder diffraction data were recorded under ambient conditions in Bragg-Brentano geometry with a Bruker D8 Advance diffractometer with CuKα$_1$ radiation (λ = 1.5406 Å).

Solution calorimetry

Enthalpies of solution were measured by using an ampoule-type isoperibolic calorimeter with a titanium reaction vessel volume of 50 cm^3.[15] The automated control scheme allowed the temperature to be maintained with an accuracy greater than 6×10^{-4} K. The temperature and thermal sensitivities of the calorimeter measuring cell were 10^{-4} K and 10^{-3} J, respectively. The instrumental errors were 0.6–1%. The accuracy of weight measurements corresponded to $\pm 10^{-5}$ g. Due to small values of the solution heat effects, a correction ($q(T)$) was introduced to account for the heat of breaking of the ampoule and evaporation of the solvent in the ampoule free volume: q(293.15 K) = 0.034 J, q(303.15 K) = –0.018 J, q(318.15 K) = –0.059 J. Other corrections were negligibly small. The calorimeter was calibrated using KCl (Merck analysis grade >99.5%) in water over a wide concentration interval with more than 20 measurements made. The obtained standard value of solution enthalpy was 17240 ± 36 J·mol^{-1}, which is in good agreement with the value 17241 ± 18 J·mol^{-1} recommended by IUPAC.[16] A minimum of four measurements were performed for each of the analyzed samples.

The enthalpy of formation, $\Delta H_f^T(AB)$, of a co-crystal with 1:1 stoichiometry can be calculated as:[17]

$$\Delta H_f^T(AB) = \Delta H_{sol}^T(A)_B + \Delta H_{sol}^T(B)_A - \Delta H_{sol}^T(AB)_B \qquad (1)$$

where $\Delta H_{sol}^T(A)_B$ and $\Delta H_{sol}^T(B)_A$ are the heats of solution for solid A in a solution containing B and solid B in a solution containing A, respectively. It is essential to consider that the enthalpy of solution of one of the pure solid co-formers may be affected by the presence of the other co-former in solution. Thus, measurements of the heat of solution taken in the presence of the second co-former are required. This ensures that the same solute A-solute B interactions that occur during co-crystal dissolution are accounted for in the calculation of the enthalpy of formation. For [**Fel+BP**] (2:1), the enthalpy of formation was calculated in a similar manner, taking appropriate account of the co-crystal stoichiometry. All experiments were conducted at T = 298.15 K. Methanol was chosen as the solvent, because the co-crystals dissolve well with a large endothermic heat effect.

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 of 10 Kmin^{-1} in an Ar atmosphere and cooled with liquid N_2. The temperature calibration of the DSC 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.

Results and discussion

Crystal structures

Crystallographic data are summarized in Table 1, and the molecular units of the co-crystals are shown in Fig. 2. In each structure, the asymmetric unit contains **Fel** and **BP** molecules connected by N–H···N hydrogen bonds. In both polymorphs of [**Fel+BP**] (1:1), the molecules are linked into discrete pairs, with only one N atom of each **BP** molecule accepting a hydrogen bond. In [**Fel+BP**] (2:1), the **BP** molecule accepts N–H···N hydrogen bonds from two **Fel** molecules to form a trimeric unit across a crystallographic inversion center (Fig.2).

In [**Fel+BP**] (1:1) form I, the 1,4-dihydropyridine ring of felodipine lies approximately in the same plane as the **BP** pyridine ring to which it is hydrogen-bonded (angle between least-squares planes *ca* 1.5°, Fig. 2a). The **BP** molecule is approximately planar, with its two pyridine rings forming an angle of *ca* 4.6°. The **BP** molecule is approximately planar, with its two pyridine rings forming an angle of *ca* 4.6°.

Table 1 Crystallographic data for the co-crystals

	[Fel+BP] (1:1) form I	[Fel+BP] (1:1) form II	[Fel+BP] (2:1)
CCDC	994273	994275	994274
Empirical formula	$C_{18}H_{19}Cl_2NO_4 \cdot C_{10}H_8N_2$	$C_{18}H_{19}Cl_2NO_4 \cdot C_{10}H_8N_2$	$(C_{18}H_{19}Cl_2NO_4)_2 \cdot C_{10}H_8N_2$
T (K)	150	150	150
Crystal system	triclinic	orthorhombic	Triclinic
Space group	*P*–1	*Fdd2*	*P*–1
a (Å)	7.7589(10)	36.197(3)	10.4207(9)
b (Å)	9.2634(12)	36.436(3)	10.6061(9)
c (Å)	17.830(2)	8.0228(6)	11.2328(9)
α (°)	90.403(8)	90	67.167(4)
β (°)	90.275(9)	90	73.749(4)
γ (°)	97.322(9)	90	81.109(5)
Volume (Å^3)	1271.0(3)	10581.1(15)	1097.0(2)
Z / Z'	2 / 1	16 / 1	1 / 0.5
Calculated density (g cm^{-3})	1.412	1.357	1.400
Absorption coeff. (mm^{-1})	0.296	0.285	0.329
F(000)	564	4512	482
Crystal size (mm)	0.35 × 0.30 × 0.20	0.35 × 0.25 × 0.10	0.35 × 0.10 × 0.05
Data collected	13673	21047	23260
Unique data	4214	4259	4000
R_{int}	0.054	0.043	0.041
Observed data [I>2σ(I)]	2594	3396	2771
$R1$ [I>2σ(I)]	0.096	0.046	0.072
w$R2$ (all data)	0.264	0.108	0.219
Goodness-of-fit (on F^2)	1.13	1.05	1.06

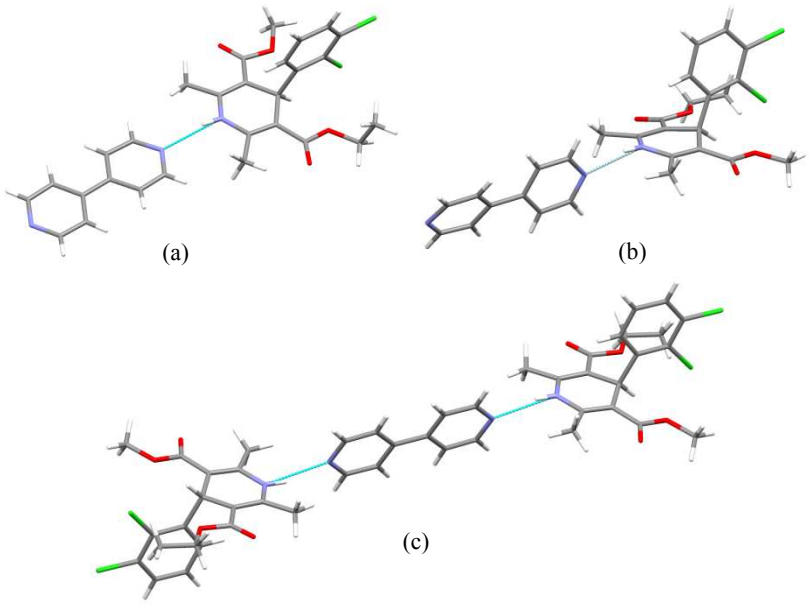


Fig.2 Molecular units in (**a**) [**Fel+BP**] (1:1) form I; (**b**) [**Fel+BP**] (1:1) form II;(**c**) [**Fel+BP**] (2:1)

This conformation allows **BP** to form both "face-to-face" contacts with neighboring 1,4-dihydropyridine rings and "side-on" contacts with the dichlorobenzene rings of felodipine (Fig. 3a). The packing arrangement of [**Fel+BP**] (1:1) form I can be described as layers of [**Fel+BP**] units in the (001) planes. Each layer contains **Fel** molecules of one enantiomer only, and neighboring layers are related by inversion symmetry. The layers are segregated so that there are clear regions with interactions between **BP** and **Fel**, and regions where only **Fel** molecules interact. In [**Fel+BP**] (1:1) form II, the 1,4-dihydropyridine ring of **Fel** and the hydrogen-bonded pyridine ring of **BP** form an angle of *ca* 77.3° (Fig. 2b). The molecular conformation of **BP** is considerably twisted from planarity, with the angle between the least-squares planes of the pyridine rings being *ca* 21.0°. This promotes "face-to-face" contacts between **BP** and the 1,4-dihydropyridine fragment of **Fel**. In this case, the structure does not show any clear segregation of the molecules as in form I. Layers can be envisaged in the (100) planes, consisting of alternating **Fel** and **BP** molecules forming hydrogen bonds to the neighboring layer (Fig. 3b).

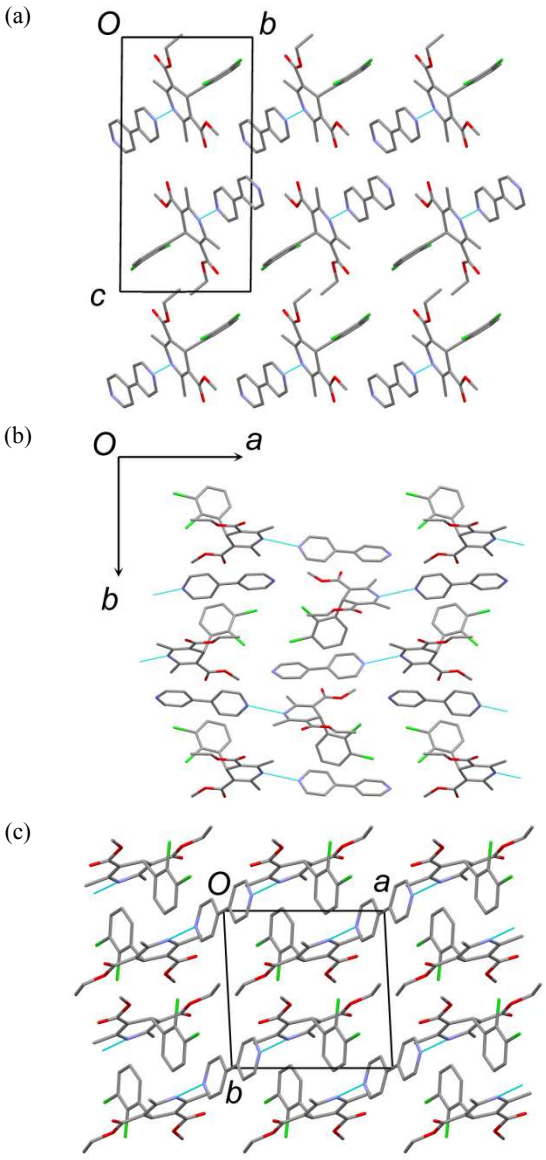


Fig.3 Molecular packing projections for (**a**) [**Fel**+**BP**] (1:1) form I, (**b**) [**Fel**+**BP**] (1:1) form II, (**c**) [**Fel**+**BP**] (2:1). H atoms are omitted.

In [**Fel+BP**] (2:1), the angle between the least-square planes of the 1,4-dihydropyridine fragment of **Fel** and the pyridine ring of **BP** is comparable to that in [**Fel+BP**] (1:1) form II (75.6°), while the **BP** molecule is planar (Fig. 2c). Centrosymmetric "back-to-back" interactions are observed between **Fel** molecules (Fig. 3c). This interaction is not seen in the [**Fel+BP**] (1:1) polymorphs, but it is one of the main structural features in the polymorphs of pure felodipine [7]. The interplanar distance for these "back-to-back" contacts (3.80 Å) in [**Fel+BP**] (2:1) is also comparable to that in the **Fel** polymorphs I-IV (3.65–3.87 Å). In addition, neighboring dichlorobenzene rings form face-to-face contacts which are similar to those in felodipine form I (Fig. 4). The dichlorobenzene rings in [**Fel+BP**] (2:1) are interspersed with **BP** molecules, forming "face-to-face" interactions (Fig. 3c).

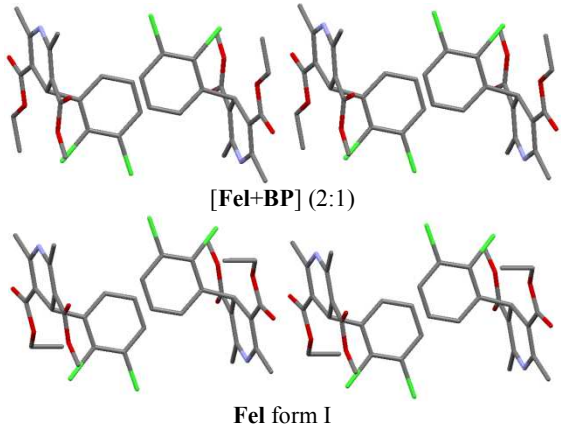


Fig.4 Similarity of "back-to-back" and "face-to-face" arrangements of felodipine molecules in the [**Fel**+**BP**] (2:1) co-crystal and **Fel** form I. H atoms and **BP** molecules are omitted.

Conformational analysis

In our previous work, attention was paid to the molecular conformation of felodipine in the known polymorphs and solvates.[6] In [**Fel+BP**] (1:1) form I, the **Fel** conformation is virtually identical to that in form I of pure felodipine, whereas the conformation of **Fel** in [**Fel+BP**] (1:1) form II and [**Fel+BP**] (2:1) corresponds to form II of pure felodipine as well as the solvates with dimethylacetamide and dimethylethyleneurea. This suggests that the [**Fel+BP**] co-crystals contain a relatively low-energy molecular conformation of felodipine.

On the other hand, the **BP** molecule shows considerable conformational variation in the three co-crystals. This reflects the relatively low energy barrier for rotation around the central C–C bond, and the high conformational flexibility of **BP** allows it to adopt a suitable orientation for different supramolecular surroundings. Gas-phase quantum chemical calculations have indicated that the minimum conformational energy for **BP** corresponds to a dihedral angle of 38.6° between the pyridine rings, with the planar conformation calculated to be *ca* 6.3 kJ mol^{-1} less stable.[18] A search of the CSD for crystal structures of **BP** co-crystals yields 131 two-component co-crystals composed of organic molecules (CSD refcodes listed in Table S1 of Supporting information).[19] Fig. 5 shows the distribution of the central dihedral angle in **BP** from the retrieved CSD set.

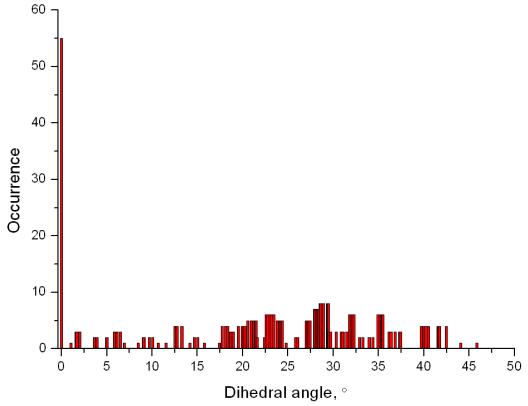
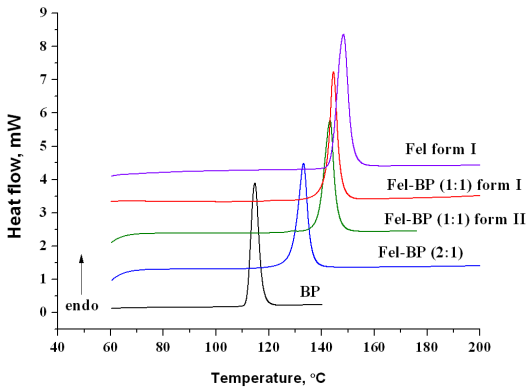


Fig.5 Distribution of the dihedral angle in **BP** molecules for two-component co-crystals retrieved from the Cambridge Structural Database.

The distribution shows clearly that the planar conformation is the most frequent one, despite the fact that it is a relatively higher-energy state. The remaining dihedral angle values are distributed uniformly, apart from a small peak around *ca* 30°, which is close to the calculated conformational energy minimum. The fact that the minimum-energy conformation is rare in the co-crystals indicates that the conformation of **BP** in a co-crystal is under the influence of its supramolecular surroundings. The packing energy gained in the case of the planar conformation must be greater than the conformational energy penalty caused by the deviation of the molecule from its optimal geometry.

Thermal analysis

The DSC traces for all of the co-crystals are shown in Fig.6, and the thermal data are tabulated in Table 2. Detailed thermal analyses of the pure felodipine polymorphs and its solvates have been reported previously.[6a,b]



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ig.6 DSC curves of the co-crystals, 4,4′-bipyridine and felodipine (form I) recorded at 10°C·min^{-1} heating rate.

Table 2 Thermophysical data for the felodipine co-crystals, with comparison to felodipine form I and 4,4′-bipyridine

	T_{fus}, °C (onset)	ΔH_{fus}, kJ mol^{-1}	ΔS_{fus}, J mol^{-1}K^{-1}
[**Fel+BP**] (1:1) form I	141.8 ± 0.2	52.1 ± 0.4	125.5
[**Fel+BP**] (1:1) form II	138.8 ± 0.2	50.5 ± 0.5	122.6
[**Fel+ BP**] (2:1)	128.9 ± 0.2	43.0 ± 0.5	107.0
Felodipine form I	143.8 ± 0.2	31.5 ± 0.5	75.9
4,4′- bipyridine	111.8 ± 0.2	24.7 ± 0.5	64.1

DSC thermograms show only one major endotherm for all of the co-crystals which corresponds to the melting process. The polymorphs of [**Fel+BP**] (1:1) melt without other phase transitions. The difference in onset temperature between the two forms is *ca* 3°C, but [**Fel+BP**] (2:1) shows a melting temperature *ca* 13°C lower. Since both the melting temperature and the enthalpy of fusion of [**Fel+BP**] (1:1) form II are lower than that of form I, form I is considered to be thermodynamically most stable.[20] Forms I and II of [**Fel+BP**] (1:1) are monotropically related.

The melting temperature of [**Fel+BP**] (1:1) form I is only *ca* 2°C lower than those of forms I and III of pure felodipine, and *ca* 7°C higher than felodipine form II. It seems that the intermolecular interactions (including hydrogen bonds), which are responsible for the thermal stability of the pure felodipine crystals, are energetically comparable to those in the [**Fel+BP**] (1:1) co-crystal. As mentioned above, the crystal structures of [**Fel+BP**] (2:1) and felodipine form I have similar arrangements of the main felodipine-felodipine contacts (apart from hydrogen bonds). However, the melting temperature of the (2:1) cocrystal is *ca* 15°C lower than that of felodipine form I. This illustrates the impact of the hydrogen bonding on the thermal stability of the crystal when other intermolecular interactions are comparable.

It might be reasonable to assume that similar regularities may be observed for 4,4′-bipyridine co-crystals with other APIs. Fig. 7 a,b shows the melting temperature of API-**BP** co-crystals as a function of the melting points of the corresponding pure APIs, taken from the retrieved CSD set.

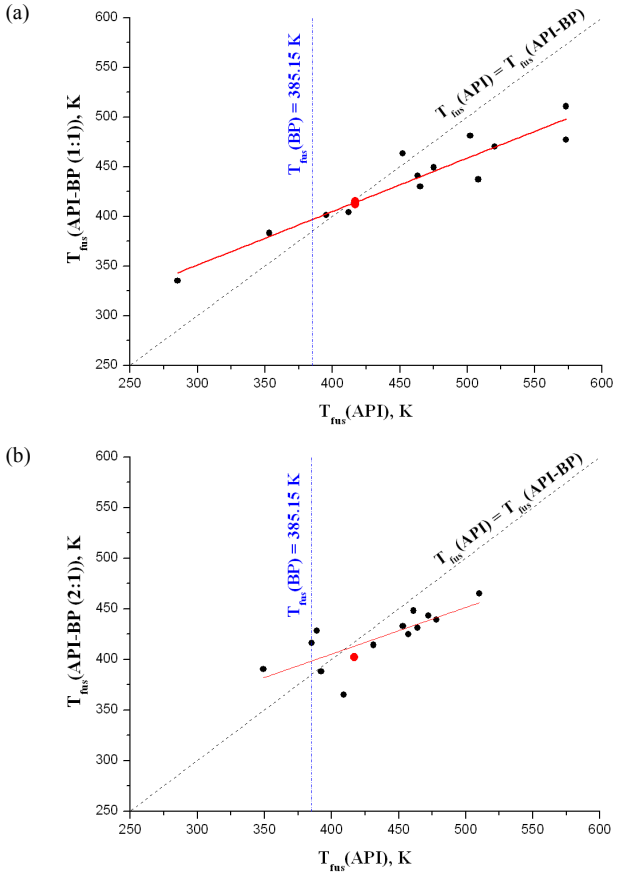

Fig.7 Plot of melting temperature for API-4,4′-bipyridine co-crystals with **(a)** 1:1 molar ratio and **(b)** 2:1 molar ratio *vs* API melting temperature. Points corresponding to the felodipine co-crystals are colored in red.

For co-crystals with a 1:1 ratio (Fig.7a), a good correlation is observed (R = 0.946). It is evident that in the temperature range considered, the increase in T_{fus} of the co-crystals is accompanied by an increase in the melting temperature of the pure API. Therefore, the **BP** molecule introduces a "constant" contribution to the thermal stability of a co-crystal, independent of the API structure. For systems with T_{fus}(API) > T_{fus}(**BP**), the melting temperature of the co-crystal is lower than that of the API, while for T_{fus}(API) < T_{fus}(**BP**), the **BP** molecule increases the melting temperature of the co-crystal compared to the pure API. In Fig.7a, the correlation line intersects the T_{fus}(API) =

T_{fus}(API+**BP**) line at *ca* 415 K (142 °C), which is approximately the melting temperature for [**Fel+BP**] (1:1) form I and for pure felodipine form I. For API-**BP** co-crystals with a 2:1 molar ratio, the correlation coefficient is considerably lower compared to the 1:1 systems (R = 0.768, Fig.7b). Probably, the melting point values of 2:1 co-crystals are more sensitive to the API-API interactions. The general trend, however, remains unchanged: T_{fus} of the co-crystal increases as T_{fus} of the API increases.

Solution calorimetry

In spite of great interest in the structure, preparation and properties of co-crystals, relatively little data exist on their thermodynamic properties, which are fundamental measures of their stability.[17,21] In order to compare the crystal lattice energies of the [**Fel+BP**] (1:1) co-crystal polymorphs and to establish the thermodynamic characteristics for formation of the co-crystals, solution calorimetry experiments were carried out. The results are summarized in Table 3 (see Tables S2 and S3 in the Supporting Information for the full data set).[**Fel+BP**] (1:1) form I is thermodynamically the most stable, while the crystal lattice energy of [**Fel+BP**] (1:1) form II is found to be 2.3 ± 0.5 kJ·mol^{-1} less stabilizing than form I. The DSC results agree with the calorimetric data qualitatively. The difference in heat of fusion between the two forms (at T_{fus}) is 1.6 ± 0.9 kJ·mol^{-1}. The ΔH^0_{tr} values for the [**Fel+BP**] (1:1) polymorphs and the polymorphs of pure felodipine are comparable.[6a] Small values for the enthalpy of formation indicate that the packing energy gain for the co-crystals is derived only from weak van der Waals forces. A similar conclusion has been proposed by Oliveira *et al.*, who studied carbamazepine, cyheptamide and dihydrocarbamazepine co-crystals with saccharin.[17] Their values of ΔH_f have the same order of magnitude: from –10.1 ± 0.9 kJ·mol^{-1} for carbamazepine-saccharin to –1.9 ± 1.1 kJ·mol^{-1} for dihydrocarbamazepine-saccharin. In the case of [**Fel+BP**] (2:1), the enthalpies of formation suggest that this co-crystal should be less thermodynamically stable than [**Fel+BP**] (1:1) form I at ambient conditions and more stable than [**Fel+BP**] (1:1) form II.

Grinding experiments

The thermodynamic stability of the [**Fel+BP**] co-crystals was also studied using mechanochemical neat grinding and solvent-drop grinding techniques.[22] Grinding experiments with stoichiometric amounts of **Fel** and **BP** in a 1:1 molar ratio in the presence of acetone, methanol or acetonitrile resulted in the formation of only [**Fel+BP**] (1:1) form I. Using a 2:1 molar ratio, the result remained practically unchanged: powder X-ray diffraction showed that a minimal amount of the [**Fel+BP**] (2:1) co-crystal was formed together with [**Fel+BP**] (1:1). Neat grinding of [**Fel+BP**] (1:1) form II resulted in transformation to form I. Thus, the results suggest that [**Fel+BP**] (1:1) form I is the thermodynamically more stable solid form, in agreement with the DSC and solution calorimetry experiments.

Hirshfeld Surfaces Analysis

Analysis of Hirshfeld surfaces is found to be a useful tool for description of various types of intermolecular contacts in molecular crystals.[23] The method has been widely used for polymorphs,[24] solvates[25] and co-crystals of APIs.[3a,26] The 3-D Hirshfeld surfaces and derived 2-D fingerprint plots are especially helpful for closely related systems, where differences in the distribution of the main intermolecular interactions are not immediately obvious. The 2-D fingerprint plots and the relative contribution of the important intermolecular contacts of Fel in the [**Fel+BP**] co-crystals are compared to those of felodipine (form I) in Fig.8. For all of the co-crystals, the H···H contacts make the most significant contribution to the total Hirshfeld surfaces, which indicates that the crystal structures are mainly stabilized by van der Waals interactions. The H···H contacts cover a broad range of distances, with the closest contacts observed between the methyl and ethyl groups of felodipine in [**Fel+BP**] (2:1). A substantial part of each Hirshfeld surface is occupied by C–H···π (C···H) contacts (11.7–19.8%), which are seen as "wings" in the 2-D fingerprint plot at *ca* 2.9–3.1 Å. The main acceptor of such contacts is the dichlorophenyl ring of felodipine. The π···π (C···C) contacts have a relatively small contribution. In [**Fel+BP**] (2:1), they reach *ca* 4% via the "back-to-back" and "face-to-face" interactions described earlier. The N···H contacts corresponding to the hydrogen bonds between **Fel** and **BP** are the shortest contacts in all of the co-crystals. A significant part of the Hirshfeld surface is also occupied by O···H interactions, which comprise *ca* 11%. These contacts are evident for [**Fel+BP**] (1:1) form I as two distinct spikes in the 2-D fingerprint plots, while for [**Fel+BP**] (1:1) form II and [**Fel+BP**] (2:1) they are less localized and observed at longer distances. In both [**Fel+BP**] (1:1) polymorphs, the closest O···H contacts occur between the carbonyl O atom of the methyl ester group of felodipine and H atoms of the neighbouring **BP** molecule (see Fig. S1 in Supporting Information). A further important interaction type in the co-crystals is Cl···H, which comprise 11–18% of the Hirshfeld surface. These contacts are most prominent in [**Fel+BP**] (1:1) form I, while in [**Fel+BP**] (1:1) form II and [**Fel+BP**] (2:1), they spread out over a wider range of distances.

Table 3 Solution enthalpies, ΔH^0_{sol}, (in methanol), enthalpy of polymorphic transition, ΔH^0_{tr}, and calculated enthalpies of formation, ΔH^0_f, at 298 K (kJ mol^{-1})

	$\Delta H^0_{sol}(Fel+BP)$	$\Delta H^0_{sol}(Fel)_{bipy}$	$\Delta H^0_{sol}(BP)_{Fel}$	$\Delta H^0_f(Fel+BP)$
[Fel+BP] (1:1) form I	43.8 ± 0.3	21.3 ± 0.1	17.4 ± 0.1	–5.2 ± 0.6
[Fel+BP] (1:1) form II	41.5 ± 0.2			–2.9 ± 0.5
ΔH^0_{tr} (form I→form II)	2.3 ± 0.5			
[Fel+BP] (2:1)	36.0 ± 0.2	21.3 ± 0.3	21.6 ± 0.1	–3.9 ± 0.6

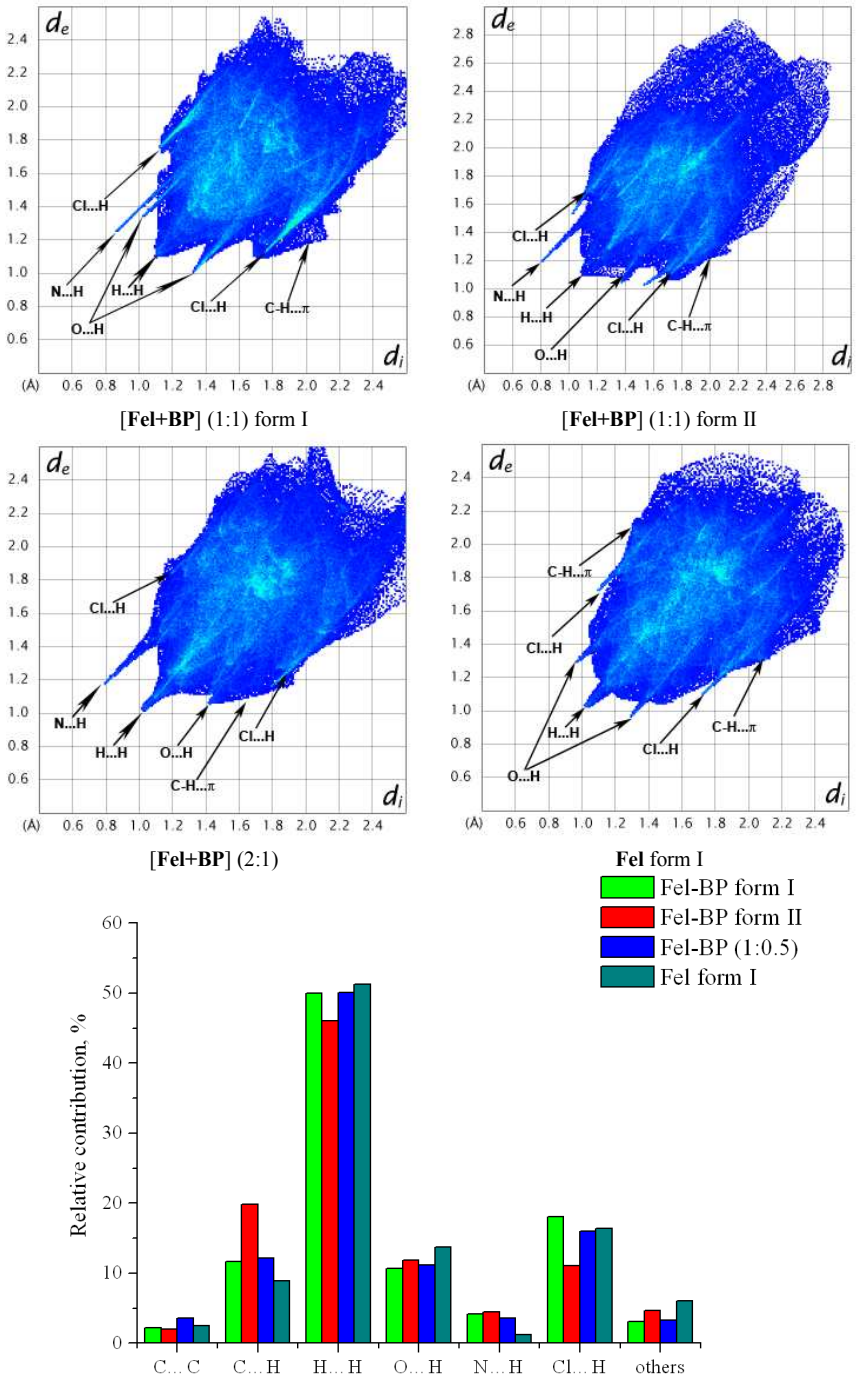

Fig.8 2-D fingerprint plots for the felodipine molecule in the co-crystals and **Fel** form I. The lower diagram shows the relative contribution of the intermolecular contacts to the Hirshfeld surface area.

An analogous Hirshfeld surface analysis was performed for pure felodipine form I. Fig. 8 shows that the distribution of the main intermolecular contacts is essentially similar to that in the co-crystals. The contribution of the H···H contacts remains at the same level, comprising essentially half of the total surface. In spite of the presence of N–H···O hydrogen bonds in **Fel**, the relative contribution of O···H interactions is only slightly larger than in the [**Fel+BP**] co-crystals, indicating that the majority of these contacts are derived from C–H···O interactions. A significant difference is observed for the N···H interactions, whose contribution is more than three times higher in the co-crystals compared to Fel, on account of the N–H···N hydrogen bonding in the former. The similarity of the Hirshfeld surfaces confirms an assumption that all intermolecular contacts present in the pure **Fel** crystal (including hydrogen bonds) are effectively compensated in the [**Fel+BP**] co-crystals, which is qualitatively consistent with the thermochemical results.

Conclusions

Co-crystals of felodipine with 4,4′-bipyridine, namely [**Fel+BP**] (2:1) and two polymorphs of [**Fel+BP**] (1:1), were obtained and

their crystal structures were determined. A CSD survey and literature analysis show that high conformational flexibility of 4,4′-bipyridine allows it to adopt a suitable orientation for different supramolecular surroundings and, therefore, contribute to the stability of a co-crystal *via* efficient formation of van der Waals interactions. It has been shown in general that the melting temperatures of API–**BP** co-crystals are effectively correlated with the melting points of the constituent APIs. Thus, the 4,4′-bipyridine molecule introduces a "constant" contribution to the thermal stability of a co-crystal, independent of the API structure. The results of DSC and solution calorimetry experiments show that [**Fel+BP**] (1:1) form I is thermodynamically the most stable co-crystal. The enthalpies of formation of the co-crystals are small, which indicates that the packing energy gain is derived only from weak van der Waals interactions. The Hirshfeld surfaces demonstrate that there is no significant difference in the distribution of the main intermolecular contacts between the [**Fel+BP**] cocrystals and form I of pure felodipine. This suggests that formation of the [**Fel+BP**] co-crystals from the individual components is mainly accompanied by rearrangement of the van der Waals interactions.

Acknowledgements

This work was supported by a Grant from the President of the Russian Federation no. MK- 67.2014.3 and Russian Foundation for Basic Research (project № 14-03-31001). We thank "the upper Volga region centre of physicochemical research" for technical assistance with DSC and XRPD experiments.

Notes and references

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† Electronic Supplementary Information (ESI) available: refcodes list used for CSD survey, the full data set of the solution calorimetry experiments, the experimental PXRD patterns, illustration of the closest O···H contacts in [**Fel+BP**] (1:1) form I and [**Fel+BP**] (1:1) form II, displacement ellipsoids at 50% probability for molecular units of the co-crystals. See DOI: 10.1039/b000000x/

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