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Diversity of felodipine solvates: structure and physicochemical properties

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Solvates of the calcium-channel blocking agent felodipine with three structurally related common organic solvents, acetone (ATN), dimethyl sulfoxide (DMSO) and acetophenone (APN), are described. A relationship between the felodipine packing arrangement in all known solvates and the van der Waals volume of the solvent molecule is established. Intermolecular interaction energies in the crystals are examined using the PIXEL approach in order to rationalize the difference between alternative molecule packing arrangements. DSC studies show that the desolvation onset temperatures of the solvates are closely comparable, despite the large difference in the boiling points of the solvent molecules. The enthalpies of formation derived from the calorimetric data for the solvates are also found to be similar, despite the difference in the van der Waals volume of the solvent molecules.

Introduction

In many cases, active pharmaceutical ingredients (APIs) are established to exist in different crystal forms such as polymorphs or solvates/hydrates.1 The latter in general play a significant part in drug development, and solid-form screening to identify solvates/hydrates is a crucial prerequisite for consistent manufacturing and processing of drugs.2 Accidental solvate formation 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. On the other hand, solvates of APIs with pharmaceutically relevant solvents can improve some physicochemical properties of drugs, such as solubility and dissolution rate.3 Moreover, desolvation of solvates can be a method to discover and prepare new polymorphic forms that may be inaccessible via ordinary crystallization techniques.4

In this paper, we focus on studying the structures and physicochemical properties of solvates of the API felodipine with three structurally related common organic solvents, acetone (ATN), dimethyl sulfoxide (DMSO) and acetophenone (APN). Felodipine [systematic name: ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate] belongs to a family of dihydropyridine calcium channel blockers that are used for treatment of hypertension and regulation of arterial pressure (Fig. 1).5

Four polymorphic forms of felodipine have been identified to date: forms I and II have been known for a long time,6 and we have quite recently reported forms III and IV.7 Polymorphism of felodipine co-crystals with 4,4'-bipyridine in 1:1 and 2:1 molar ratios has been studied,8 and a hydrated co-crystal of felodipine with diazabicyclo[2.2.2]octane (DABCO) has also been reported.9 In addition, felodipine exhibits a strong propensity for solvate formation with various solvents. The solvate of felodipine with acetone was described and characterized for the first time by Rollinger and Burger10 using DSC, IR spectroscopic and powder X-ray diffraction techniques. However, a single-crystal X-ray structure of the solvate has not previously been reported. The crystal structure of a felodipine solvate with formamide ([Fel+FA]) has been published by Lou et al.,11 and two solvates with dimethylformamide (DMF) and N-methylformamide (N-MeFA) have been studied by Perlovich et al.12 We have also reported felodipine solvates with the structurally-related high-boiling point solvents, dimethylacetamide (DMAA), dimethylethyleneurea (DMEU) and tetramethylurea (TMU).13 In this work, we consider all experimental data obtained so far in a systematic manner, with an aim to rationalize the relationships between the crystal structures of the solvates and their observed physicochemical properties, which is an important issue in a pharmaceutical solid-form development.

![Fig.1 Structure of felodipine and investigated solvent molecules with atom numbering.](image-url)
Material and Methods

Compounds and solvents

Felodipine (C_{20}H_{28}Cl_{6}NO_{4}, MW 384.26, 99.5%, racemate) was produced by Xiamen (Fine Chemical Import @ Export Co., LTD) and received as crystalline form I. All solvents were purchased from Sigma-Aldrich (Denmark). All of the starting materials were used without further purification.

Crystallization procedure

The solvates of felodipine with dimethyl sulfoxide and acetophenone were prepared by dissolving felodipine in each respective solvent preheated to 60°C. The obtained clear solution was slowly cooled and then allowed to evaporate under ambient conditions. Single crystals of the felodipine solvate with acetone were obtained by slow evaporation of a saturated felodipine solution stored at -20°C in a freezer. Crystals obtained from the crystallization batches were air dried before being subjected to further analysis.

X-ray diffraction

Single-crystal X-ray diffraction data for [Fel+ATN] and [Fel+APN] were collected on a Bruker-Nomius X8-APEXII CCD diffractometer using MoKα radiation (λ = 0.7107 Å) at 150(1) K. Data for [Fel+DMSO] were collected under ambient conditions using a Bruker P4 diffractometer with MoKα radiation (λ = 0.7107 Å). The structures were solved by direct methods and refined by full matrix least-squares on F² with anisotropic thermal parameters for all non-hydrogen atoms.

Aqueous dissolution measurements

Dissolution measurements were carried out by the shake-flask method at 25.0 ± 0.1°C. Samples were suspended in 10 ml of water in glass tubes. The amount of felodipine solvate dissolved was measured by taking aliquots of 2 ml of the respective media and measuring concentration in a UV-vis spectrophotometer (Cary 50, Varian Inc.). The solid phase was removed by isothermal filtration (VWR syringe filter, PTFE, 0.45 μm). The results are stated as the average of at least three replicated experiments.

Solution calorimetry

Enthalpies of solution were measured by using an ampoule-type isoperibolic calorimeter with a titanium reaction vessel volume of 50 cm³. 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 ±0.01 mg. Due to small values of instrumental errors, the accuracy of weight measurements was ±0.6–1%. The accuracy of weight measurements was ±0.001 mg. Due to small values of instrumental errors, the accuracy of weight measurements was ±0.6–1%. The accuracy of weight measurements was ±0.001 mg. Due to small values of instrumental errors, the accuracy of weight measurements was ±0.6–1%

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Differential scanning calorimetry (DSC)

Thermal analysis was carried out on a DSC 204 F1 Phoenix differential scanning heat flux calorimeter (NETZSCH, Germany) with a high sensitivity µ-sensor. The sample was heated at a rate of 10°C·min⁻¹ in an Ar atmosphere over the temperature range of 25 to 170-180°C and cooled with gaseous N₂. The temperature calibration was performed against six high-purity substances: cyclohexane (99.96%), Hg (99.99%), biphenyl (99.5%), In (99.999%), Sn (99.999%), and Bi (99.999%). The accuracy of the weighing procedure was ±0.01 mg.

Thermogravimetric analysis (TGA)

TGA was performed on a TG 209 F1 Iris thermomicrobalance (Netzsch, Germany). Approximately 10 mg of the sample was added to a platinum crucible. The samples were heated over the temperature range of 25 to 250°C at a constant heating rate of 10°C·min⁻¹. The samples were purged with a stream of flowing dry Ar throughout the experiment at 30 mL·min⁻¹.

Hot stage microscopy (HSM)

Thermomicroscopic investigations were performed with an optical polarizing microscope (Altami Polar 312) equipped with a hot stage and Microstat 100 temperature controller. The microscope images were recorded with an Altami CMOS digital camera using Altami Studio image capture software. The samples were heated over a temperature range of 25–170°C at a constant heating rate of 2°C·min⁻¹. The hot stage was calibrated using USP melting point standards (vanillin, acetonilide, phenacetin, caffeine).

Computational procedures

The van der Waals molecular volume (V_{vdm}) in the crystal lattice was calculated using the spatial descriptors in Materials Studio. Intermolecular interaction energies were analyzed using the PIXEL approach developed by Gavezzotti. This method provides quantitative determination of crystal lattice energies and pairwise intermolecular interactions, with a breakdown of these energies into coulombic, polarization, dispersion and repulsion terms.

Results and Discussion

Crystal structures

Crystallographic data are summarized in Table 1, and the molecular units of the solvates are shown in Fig. 2. In each structure, the solvent molecule accepts an N–H···O hydrogen bond from the felodipine molecule. In the [Fel+DMSO] solvate, the S atom of the solvent molecule is disordered over two positions, with the major component having a site-occupancy factor of 0.857(6) (Fig.2a). The O atom (involved in the hydrogen bond) and the C atoms of the methyl group occupy consistent positions. This type of disorder is common in DMSO solvates. According to Cruz-Cabeza et al., almost 50% of DMSO solvate structures found in the Cambridge Structural Database show structural disorder. The ester groups of felodipine also show some disorder, corresponding to exchange of the positions of the...
The solvent molecule of [Fel+APN] is fully ordered and the plane of the APN molecule forms an angle of ca 12° with the 1,4-dihydropyridine ring (Fig.2b). For the [Fel+ATN] solvate, the 1,4-dihydropyridine ring of Fel and the plane of the hydrogen-bonded ATN molecule form an angle of ca 9.4° (Fig. 2c).

In our previous works, attention has been paid to the molecular conformation of felodipine in the known polymorphs, co-crystals and solvates.\(^{7,8,13}\) The molecular conformation of felodipine is essentially identical in [Fel+ATN] and [Fel+DMSO], and it corresponds to a relatively low-energy molecular conformer, which is observed in the most of the known felodipine solvates. In [Fel+APN], the OMe ester group adopts an opposite orientation, so that the C=O group points away from the Me group of the 1,4-dihydropyridine ring. This conformation is found to be similar to that in [Fel+TMU] and [Fel+FA] (see details in the Supporting Information).

In the [Fel+DMSO] solvate, the Fel molecules are packed in a centrosymmetric “back-to-back” manner, which is one of the main structural features in the polymorphs of pure felodipine (see Figs. S2-S4 in the Supporting Information).\(^{7}\) The interplanar distance of 3.90 Å for these “back-to-back” contacts at the longer end of those observed in felodipine polymorphs I-IV (3.65–3.87 Å). The packing arrangement of the [Fel+DMSO] solvate can be described as parallel layers of felodipine molecules (in the (01–1) planes), where the space between layers is occupied by DMSO (Fig 3a).

In the [Fel+APN] solvate, the molecules are arranged as alternating bilayers of Fel and single layers of APN molecules parallel to the (001) planes. Thus, there are clear regions with the solvent-solvent interactions and regions where only felodipine molecules interact. At the inside of each Fel bilayer, the molecules are packed in a “side-on” manner so that the dichlorobenzene rings approach the backside of the neighbouring 1,4-dihydropyridine rings. A similar packing arrangement is observed in the [Fel+TMU] solvate. In addition, C24-H24…O3
interactions are formed between the phenyl ring of APN and the OMe group of Fel (Fig 3b). In the case of the [Fel+ATN] solvate, the structure does not show any clear separation of the Fel and solvent molecules, as observed for the [Fel+APN]. The hydrogen-bonded ATN molecules are situated between the neighboring Fel molecules forming a “face-to-face” contact with the dichlorobenzene rings (Fig 3c). The crystal structure of this solvate is also based on “back-to-back” interaction between Fel molecules, as observed for the [Fel+DMSO] solvate. However, every second centrosymmetric “back-to-back” molecular pair in [Fel+APN] is turned 90° to each other to form a ladder-type structure (Fig 3d). The perpendicular orientation of the neighbouring felodipine molecules leads to formation of C8-H8…O1 and C9-H9…O3 interactions between dichlorobenzene rings and OMe/OEt groups. This type of packing arrangement is not observed in any of the other known felodipine polymorphs, solvates or co-crystals.

As mentioned in the Introduction, six solvates of felodipine are already reported in the literature. The crystal structures of the solvates (including the three new ones reported here) can be divided into two groups: those based on “back-to-back” packing arrangements of the Fel molecules and those where the units are packed in a “side-on” manner. Apparently, the Fel-Fel molecule arrangement should depend on the interaction energy between solvent and Fel as well as the spatial characteristics the solvent molecule that is present in the solvate structure. Different characteristics of the solvent molecules such as the ability to form donor-acceptor interactions and the topological similarity were tested in order to find a relationship between properties of the solvent and the crystal packing arrangement of the felodipine molecules (see details in the Supporting Information). The results, however, were not able to provide a clear answer to the question of interest. The most suitable parameter to consider is found to be the van der Waals volume ($V_{vdw}$) of the solvent molecule. Since all the solvent molecules have only one site of hydrogen bonding, this parameter is responsible for the most of the weak van der Waals interactions that occur between molecules in a crystal.

Scheme 1 illustrates the change in the crystal packing arrangement as the van der Waals volume ($V_{vdw}$) of the solvent molecule increases. It is evident that at relatively small $V_{vdw}$ (40 Å$^3 < V_{vdw} < 70$ Å$^3$) the Fel molecules tend to form a “back-to-back” packing arrangement, which is also one of the main structural features in the crystals of the non-solvated compound. Formation of a “side-on” organization is observed when the van der Waals volume of the solvent molecule is greater than 70 Å$^3$. In [Fel+DMF] and [Fel+DMAA], the neighboring Fel molecules are turned so that their dichlorobenzene rings lie approximately perpendicular to each other, while in [Fel+DMEU], the dichlorobenzene planes form an angle of ca 64°. Further increase of $V_{vdw}$ of the solvent molecule over 110 Å$^3$ also leads to modification of the packing.
arrangement within the framework of a “side-on” crystal organization. In [Fel+APN] and [Fel+TMU], the Fel molecules are arranged into double layers of centrosymmetric units. Inside of each layer the molecules are related by crystallographic translation (along a).

Thus, “side-on” and “back-to-back” structure organizations are two alternative packing arrangements for the Fel molecules in the solvates. It seems that the “side-on” interactions are less stable, since they are not seen in any of the polymorphs of pure felodipine. The stabilization of such structures is expected to be on account of differing intermolecular interactions with solvent molecules.

In order to verify this assumption, the intermolecular interaction energies in the crystal structures were calculated using the PIXEL approach of Gavezzotti\(^{16}\) (Table 2). It is evident that dispersion interactions dominate the crystal structures of all of the solvates, while the Coulombic, polarization and repulsion terms play a lesser role. There are a few exceptions: for [Fel+FA] and [Fel+N-MeFA], the contribution of the Coulombic interaction is slightly larger compared to that for the rest of the solvates due to extra hydrogen bonds formed between Fel and the solvent molecules. It should be noted that the crystal lattice energies (\(E_{\text{lat}}\)) for all of the solvates are closely comparable and independent of the packing arrangements. The average magnitude of \(E_{\text{lat}}\) for all of the crystals is found to be 111.4 kJ·mol\(^{-1}\), with a standard deviation of 5.2 kJ·mol\(^{-1}\) (4.7%).

Although the total crystal lattice energies are similar, the energy distribution between different types of molecules in the solvates is distinguishable (Fig. 4). It is evident that for the crystals with a “back-to-back” arrangement, the Fel-Fel interactions provide the largest contribution to the lattice energy, while the solvates with a “side-on” organization are mainly stabilized by Fel-Solv interactions, with the Fel-Fel term being less prominent. This supports the assumption made above that the structures based on “side-on” interactions are expected to be less stable with respect to their Fel-Fel interactions. The transformation from the “back-to-back” to the “side-on” arrangement occurs at certain value of \(V_{\text{rmsd}}\) for the solvent molecule, which is apparently large enough to stabilize the structure via more stabilizing Fel-Solv interactions. The overall similarity of the \(E_{\text{lat}}\) values indicates an effective distribution of all intermolecular interactions in the crystals so that the total lattice energies of the systems remain practically unchanged.

### Table 2

The results of PIXEL calculations: lattice energies (\(E_{\text{lat}}\)), Coulombic energies (\(E_{\text{coul}}\)), polarization energies (\(E_{\text{pol}}\)), dispersion energies (\(E_{\text{disp}}\)) and repulsion (\(E_{\text{rep}}\)) energies in kJ·mol\(^{-1}\)

<table>
<thead>
<tr>
<th>Solvate</th>
<th>(E_{\text{coul}})</th>
<th>(E_{\text{pol}})</th>
<th>(E_{\text{disp}})</th>
<th>(E_{\text{rep}})</th>
<th>(E_{\text{lat}})</th>
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<tr>
<td>[Fel+FA]</td>
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<td>27.2</td>
<td>-103.6</td>
<td>85.3</td>
<td>-115.1</td>
</tr>
<tr>
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<td>26.0</td>
<td>-109.4</td>
<td>81.5</td>
<td>-163.8</td>
</tr>
<tr>
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<td>20.8</td>
<td>-123.1</td>
<td>88.7</td>
<td>-103.4</td>
</tr>
<tr>
<td>[Fel+DMSO]</td>
<td>-52.9</td>
<td>29.8</td>
<td>-117.4</td>
<td>90.8</td>
<td>-109.4</td>
</tr>
<tr>
<td>[Fel+DMF]</td>
<td>-52.6</td>
<td>24.3</td>
<td>-110.1</td>
<td>83.9</td>
<td>-103.1</td>
</tr>
<tr>
<td>[Fel+DMAA]</td>
<td>-56.7</td>
<td>31.3</td>
<td>-128.5</td>
<td>108.5</td>
<td>-108.1</td>
</tr>
<tr>
<td>[Fel+DMEU]</td>
<td>-57.0</td>
<td>27.7</td>
<td>-138.3</td>
<td>106.7</td>
<td>-116.3</td>
</tr>
<tr>
<td>[Fel+APN]</td>
<td>-52.1</td>
<td>23.1</td>
<td>-135.5</td>
<td>95.0</td>
<td>-115.5</td>
</tr>
<tr>
<td>[Fel+TMU]</td>
<td>-53.0</td>
<td>23.6</td>
<td>-123.9</td>
<td>84.9</td>
<td>-115.6</td>
</tr>
</tbody>
</table>

**Fig. 4** The relative contributions of the intermolecular interaction energies between the different types of molecules in the solvates calculated using the PIXEL method

As a next step, all of the solvate crystal structures were compared using the Crystal Packing Similarity module\(^{19}\) implemented in Mercury,\(^{20}\) in order to identify isostructural systems. For the “back-to-back” structures, the search did not reveal any similarity involving a statistically significant number of overlaid molecules (considered to be \(n > 10\) and \(rmsd_n < 1\)). However, comparison of the crystal structures of [Fel+DMF] and [Fel+DMAA], which are “side-on” arranged, indicates that these two crystals contain the same principal substructure of the Fel molecules (\(n = 20, rmsd_n = 0.350\) Å). (see Fig. S5 in the Supporting Information). For the rest of the “side-on” structures the search did not show any further satisfactory match. Thus, only two solvates are found to be isostructural.

### Thermal analysis

In the present study, DSC, TGA and HSM were used to assess the stability of the [Fel+ATN], [Fel+APN] and [Fel+DMSO] solvate crystals. Detailed thermal analyses of the pure felodipine polymorphs and a number of different solvates have been reported previously.\(^{7, 12, 13}\) It has to be pointed out that the preparation and measurement procedures were unified for all the solvates in order to avoid the influence of those factors on the results of thermal analysis. The DSC curves are shown in Fig. 5, and the thermal data are tabulated in Table 3. For [Fel+APN] and [Fel+DMSO], DSC thermograms show only one endotherm which corresponds to the desolvation and melting processes. This thermal behaviour was found to be a common phenomenon for all of the felodipine solvates reported so far.\(^{12, 13}\) By contrast, [Fel+ATN] shows a broad desolvation peak over the range ~70-
Table 3 shows clearly that boiling points of the solvents are considerably higher than the temperatures of desolvation of the corresponding solvates. For [Fel+ATN], however, the boiling point of the solvent, which is significantly lower than that for other solvents, is found to be ca. 13.8°C lower than the desolvation temperature. In the solvates with high-boiling point liquids, the solvent does not evaporate completely as it is released from the crystal, and it partly dissolves the desolvated felodipine, as seen in HSMS experiments (Figure S6-S8 in the Supporting Information). It should be noted that the mentioned processes can affect the desolvation enthalpies derived from the DSC experiment, so direct comparison of those would not be quite correct. Weight loss measurements in the TGA analysis are consistent with the DSC and HSMS results (see Figure S9-S11 in the Supporting Information). The TGA curve for [Fel+ATN] indicates a classical one-step loss of solvent over the range ~70-90°C, while for [Fel+APN] and [Fel+DMSO], a continuous weight loss is observed over a temperature range 80–250°C. The TGA data for the latter solvates show several consecutive processes taking place during heating. The first step corresponds to loss of solvent and solvent vaporization (80-230°C), while further heating leads to Fel decomposition (above 230°C).

For all of the solvates, the enthalpies of formation derived from the calorimetric data are similar, despite the difference in the crystal packing arrangements. It should be noted that enthalpy of formation is an integral parameter which indicates the difference between the crystal lattice energy of a solvate and pure Fel. Therefore, it can be deduced that the solvates should have comparable $E_{lat}$ values, which is consistent with the PIXEL calculations.

### Analysis of Hirshfeld Surfaces

Analysis of Hirshfeld surfaces is found to be a useful tool for description of various types of intermolecular contacts in molecular crystals. The method has been widely used for polymorphs, solvates, and co-crystals of APIs. The relative contributions of the important intermolecular contacts of Fel in...
the solvates are compared to those of felodipine (Form I) in Fig. 6. The 2-D fingerprint plots for the solvates are shown in Fig. S12 in the Supporting Information.

For all of the solvates, the H···H contacts comprise approximately half of the total Hirshfeld surfaces (50.5% on average), which indicates that the crystal structures are mainly stabilized by van der Waals interactions. A substantial part of each Hirshfeld surface is occupied by the C···H, O···H and Cl···H contacts. Their relative contributions to the Hirshfeld surfaces are comparable, comprising on average 14.9% for C···H, 16.0% for O···H and 14.4% for Cl···H. The O···H contacts are the shortest ones in all of the solvates. It was noted that a ratio of the relative contributions of the main intermolecular contacts in the solvates remains practically unchanged: H···H/C···H/O···H/Cl···H ≈ 1/0.3/0.3/0.3. It might be reasonable to assume that this ratio indicates the most efficient crystal packing.

**Aqueous dissolution**

Dissolution profiles for [Fel+APN], [Fel+DMSO], the previously reported felodipine solvates and felodipine (form I) are shown in Fig. 7. For [Fel+ATN], the dissolution experiment was not performed due to its low stability at room temperature. It is seen that all of the dissolution profiles have a similar shape. In terms of the “spring and parachute” concept the dissolution profiles for the felodipine solvates show clearly a “spring” phase, while the “parachute” effect is observed only for a short time. During the first hour of dissolution, the concentration of felodipine is increased by several times compared to the form I of API. This is followed by fast crystallization of felodipine, and the latter process lasts from 1 to 6 hours depending on the solvate stability.

The experiment shows that the least stable solvate is [Fel+DMSO], while the longest life-time is observed for [Fel+APN] and [Fel+TMU].

**Conclusions**

Three new solvates of felodipine with structurally related common organic solvents, acetone, dimethyl sulfoxide and acetophenone, have been obtained and their crystal structures determined. All of the currently established solvate crystal structures can be conventionally divided into two groups with respect to the felodipine packing arrangement: structures based on “back-to-back” interactions between felodipine molecules and crystals where the molecules are arranged in a “side-on” manner. The felodipine packing arrangement is found to depend on the van der Waals volume ($V_{vdw}$) of the solvent molecule. At relatively small $V_{vdw}$ (40 Å$^3$ < $V_{vdw}$ < 70 Å$^3$) the felodipine molecules tend to form a “back-to-back” structure, while formation of the “side-on” structure is observed for $V_{vdw} > 70$ Å$^3$. PIXEL calculations reveal that in the crystals with a “back-to-back” arrangement, the Fel-Fel interactions provide the largest contribution to the lattice energy, while the solvates with a “side-on” organization are mainly stabilized by Fel-Solv interactions, with the Fel-Fel contribution being less prominent. DSC studies show that the desolvation onset temperatures of the solvates are closely comparable, despite quite large differences in the solvent boiling points. For most of the systems, the desolvation occurs in a narrow temperature range between 80 and 100°C. The enthalpies of formation derived from the calorimetric data for the solvates are found to be similar, despite the difference in $V_{vdw}$ of the solvent molecules. Analysis of Hirshfeld surfaces indicates that there is no significant difference in the distribution of the main intermolecular contacts between the solvates, and the following ratio is suggested: H···H/C···H/O···H/Cl···H ≈ 1/0.3/0.3/0.3. The aqueous dissolution profiles for all solvates demonstrate only a clear “spring” phase, while the “parachute” effect is observed over a time period from 1 to 6 hours depending on the solvate stability.

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Notes and references


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Solvates of the calcium-channel blocking agent felodipine with three structurally related common organic solvents, acetone (ATN), dimethyl sulfoxide (DMSO) and acetophenone (APN), are described. A relationship between the felodipine packing arrangement in all known solvates and the van der Waals volume of the solvent molecule is established. The solvates were investigated by a wide spectrum of experimental methods and approaches: X-ray diffraction, DSC, TG, HSM and solution calorimetry. Intermolecular interaction energies in the crystals are examined using the PIXEL approach in order to rationalize the difference between alternative molecule packing arrangements.

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