Communication

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Cryst. Growth Des., **Just Accepted Manuscript** • DOI: 10.1021/acs.cgd.8b00683 • Publication Date (Web): 12 Jun 2018

Polymorphism of Sildenafil: A new metastable desolvate

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ABSTRACT: A new anhydrous polymorph of the free base of sildenafil and two solvates (acetonitrile and propanenitrile) have been discovered and fully characterized. The new polymorph can be considered a desolvate of the acetonitrile solvate and is related to the most stable form I by morphotropism. The new polymorph can only be obtained by desolvation of the acetonitrile solvate. Thus, this study is a new example of the importance of this multicomponent family of solid forms in the discovery of new polymorphs of Active Pharmaceutical Ingredients.

INTRODUCTION

Active Pharmaceutical Ingredients (APIs) can exist in addition to polymorphs as solvates, phenomenon known as pseudopolymorphism.[1] Since APIs are small molecular weight compounds they

tend to form solvates and hydrates where solvent molecules are an integral part of the solid form structure. In particular, water molecules can occupy isolated sites (stoichiometric hydrates) or channels (stoichiometric and non-stoichiometric hydrates).[2] Frequently, the removal of water molecules produces the collapse of the crystal network with the result of an amorphous[3] form or an anhydrous polymorph.[4, 5]

Although it has been suggested that 33% of organic compounds can form hydrates but only 10% of them can form solvates[6] the formation of solvates can have important consequences during the development of an API because they can affect to their physicochemical properties such as stability or solubility in relation to the anhydrous form.[7, 8] The Cambridge Structural Database has been searched in order to study the frequency of solvate formation and more than 300 different solvent molecules were identified to form a solvate.[9] Moreover, hydrate formation in organic compounds and the important factors determining the high frequency of hydrates has been studied by analyzing the Cambridge Structural Database (CSD)[10] and statistical models for the prediction of hydrate and solvate formation have been developed.[11]

API solvates are generally prepared by recrystallization, but hydrates may also appear during formulation of a drug while exposed to air. But while pharmaceutical hydrates are viable forms for drug products because there is no safety concern about water as a crystal adduct, solvates are rarely formulated because of safety concerns due to solvent toxicity.[12,13] However, the phenomenon of pseudopolymorphism can have a significant impact in the development of a pharmaceutical drug since the pharmaceutical drugs are usually in contact with organic solvent during the purification and processing stages.[14] Particularly relevant is the case of sulfathiazole,[15] which forms over one hundred solvates.

Usually solvate structures collapse immediately after the removal of the solvent, however in some cases isomorphic desolvates are formed when the solvent molecules are removed without the collapse of the crystal network and retaining most of the packing issues of the parent solvate.[16] Thus, isomorphic

desolvates can be regarded as different polymorphs but constitute a specific category of solid forms since they can only be formed by desolvation and stabilized in the absence of solvent molecules.[17] The presence of voids in the desolvate structure is related to its usual tendency to be hygroscopic[18,19] and to a lower stability based on a reduced packing efficiency.[20] In some cases, the desolvation produces very small crystallites that although crystalline at a local level give bad-defined PXRD patterns, which hinder their characterization.[21] Although hydrates and solvates constitute a topic of continuous research interest in the pharmaceutical industry, isomorphic desolvates have been scarcely explored in the crystal engineering field to date.[22] Thus, in this paper we report a new isomorphic desolvate of the free base of sildenafil which is morphotropically related to the known anhydrous form I. The study has been complete with the full characterization of new acetonitrile and propanenitrile solvates of sildenafil, which are key to understand the role of the solvent in the discovery of the new polymorph of sildenafil.

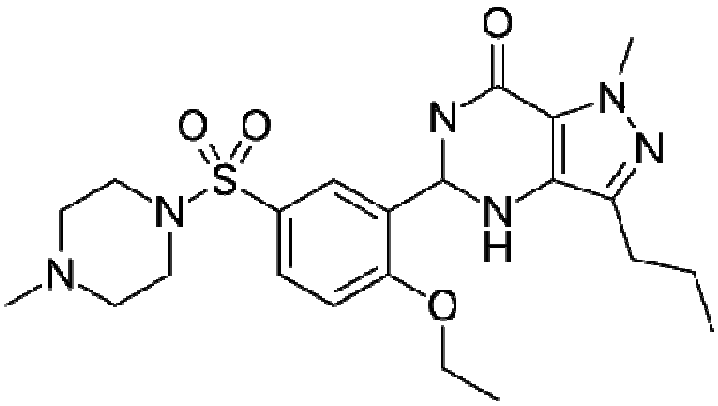

Figure 1. Molecular structure of Sildenafil.

2 MATERIALS AND METHODS

2.1. Materials

Sildenafil used in this study was of reagent grade and used as received from Polpharma (form I). Anhydrous form II has been obtained by slurring Sildenafil (form I) in ACN followed by fast drying

under vacuum (30 minutes) at 25 ºC. ACN solvate (form ACN_I) has been obtained by slow crystallization in ACN after 37 days at 25 ºC. ACN solvate (form ACN_{II}) has been obtained after keeping Sildenafil (form I) in ACN atmosphere for 2 weeks. Propanenitrile solvate has been obtained by slow crystallization in propanenitrile after 1 day at 25 ºC.

2.2 Methods

2.2.1 X-ray crystallographic analysis.

Single crystal X-ray diffraction intensity data of Sildenafil form I and acetonitrile solvate form ACN_I were collected using a D8 Venture system equipped with a multilayer monochromator and a Mo microfocus (λ = 0.71073 Å). Frames were integrated with the Bruker SAINT software package using a SAINT algorithm. Data were corrected for absorption effects using the multi-scan method (SADABS).[23] The structure was solved and refined using the Bruker SHELXTL Software Package, a computer program for automatic solution of crystal structures and refined by full-matrix least-squares method with ShelXle Version 4.8.0, a Qt graphical user interface for SHELXL computer program.[24]

Powder X-ray diffraction pattern of form II was obtained on a PANalytical X'Pert PRO MPD diffractometer in transmission configuration using Cu Kα1+2 radiation (λ = 1.5406 Å) with a focusing elliptic mirror and a PIXcel detector working at a maximum detector's active length of 3.347°. Configuration of convergent beam with a focalizing mirror and a transmission geometry with flat sample sandwiched between low absorbing films measuring from 2 to 80° in 2θ, with a step size of 0.013° and a total measuring time of 2 hours. The powder diffractogram data was perfectly indexed to a orthorhombic cell of about 4954 $Å^3$ by means of Dicvol04,[25] and the space group perfectly determined to be P *c c n* from the systematic absences. With one independent molecule of Sildenafil in the asymmetric unit, Z=8, the crystal structure was determined by direct space methodologies starting from a molecular model optimized with the commercial software SPARTAN[26] by means of the program FOX[27] with the parallel tempering algorithm. Some constraints were introduced to FOX, considering

aromatic rings as rigid groups. Several trials of 20 million runs were performed. The refinement of the structure has been performed by the Rietveld method using FullProf,[28] figure 2 depicts the final Rietveld plot. The crystal structure of anhydrous form I has been solved at room temperature from SXRD in order to compare with form II since the structures deposited at the CSD[29] have been solved at different temperatures. A summary of crystal data and relevant refinement parameters are given in Table 1.

Table 1. Crystal data and structure refinement parameters for the different forms of Sildenafil

Structure	Form I	Form II	Acetonitrile solvate form ACN_I	Propanenitrile solvate
Empirical formula	$C_{22}H_{30}N_6O_4S$	$C_{22}H_{30}N_6O_4S$	$C_{24}H_{33}N_7O_4S$	$C_{25}H_{35}N_7O_4S$
Formula Weight	474.58	474.58	515.63	529.66
Temperature (K)	302(2)	298(2)	293(2)	100(2)
Wavelength (Å)	0.71073	1.5406	0.71073	0.71073
Crystal system	Monoclinic	Orthorhombic	Orthorhombic	Monoclinic
space group	P21/c	P c c n	P c c n	P21/c
a, b, c (Å)	17.301(4) 17.072(3) 8.3324(17)	35.713(1) 17.0949(4) 8.1146(1)	17.0918(16) 37.876(4) 7.9351(7)	19.3079(9) 14.8253(6) 9.2680(4)
α, β, γ (°)	90 99.222(8) 90	90 90 90	90 90 90	90 90.720(2) 90
Volume ($Å^3$)	2429.3(9)	4954.0(2)	5136.9(9)	2652.7(2)
Z, Density (calc.) (Mg/m^3)	4, 1.298	8, 1.273	8, 1.333	4, 1.326
Absorption coefficient (mm^{-1})	0.173	-	0.171	0.167
F(000)	1008	-	2192	1128
Crystal size (mm^3)	0.275 x 0.140 x 0.108	-	0.236 x 0.148 x 0.066	0.222 x 0.124 x 0.073
θ range for data collection (°)	2.386 to 26.345	2.0 to 80 step 0.026 (2θ)	2.383 to 26.435	2.518 to 26.452
Limiting indices	-21<=h<=21, -21<=k<=21, -10<=l<=10	-	-18<=h<=21, -38<=k<=47, -9<=l<=9	-24<=h<=24, -18<=k<=18, -11<=l<=11
Reflections collected / unique	39306/4943 [R(int)=0.1201]	-	26368/5240 [R(int)=0.1755]	50725/5407 [R(int)=0.0555]
Completeness to θ= 25.242º (%)	99.9	-	99.8	99.0

Absorption correction	Semi-empirical from equivalents	-	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	0.7454 and 0.6855	-	0.7454 and 0.5871	0.7454 and 0.6943
Refinement method	Full-matrix least squares on F^2	Rietveld	Full-matrix least squares on F^2	Full-matrix least squares on F^2
Data / restraints / parameters	4943 / 0 / 310	3712/66/10	5240 / 0 / 346	5407 / 0 / 342
Goodness-of - fit on F^2	1.016		0.999	1.035
Final R indices [I > 2σ(I)]	R1=0.0543, wR2=0.1075	Rwp = 12.3	R1=0.0838, wR2=0.1638	R1=0.0446, wR2=0.1040
R indices (all data)	R1=0.1327, wR2=0.1336	Chi2 = 4.93	R1=0.2017, wR2=0.2077	R1=0.0603, wR2=0.1128
Largest diff. peak and hole (e.Å^{-3})	0.176 and -0.295		0.383 and -0.328	1.59 and -0.702
CCDC	1821370	1832582	1821373	1821372

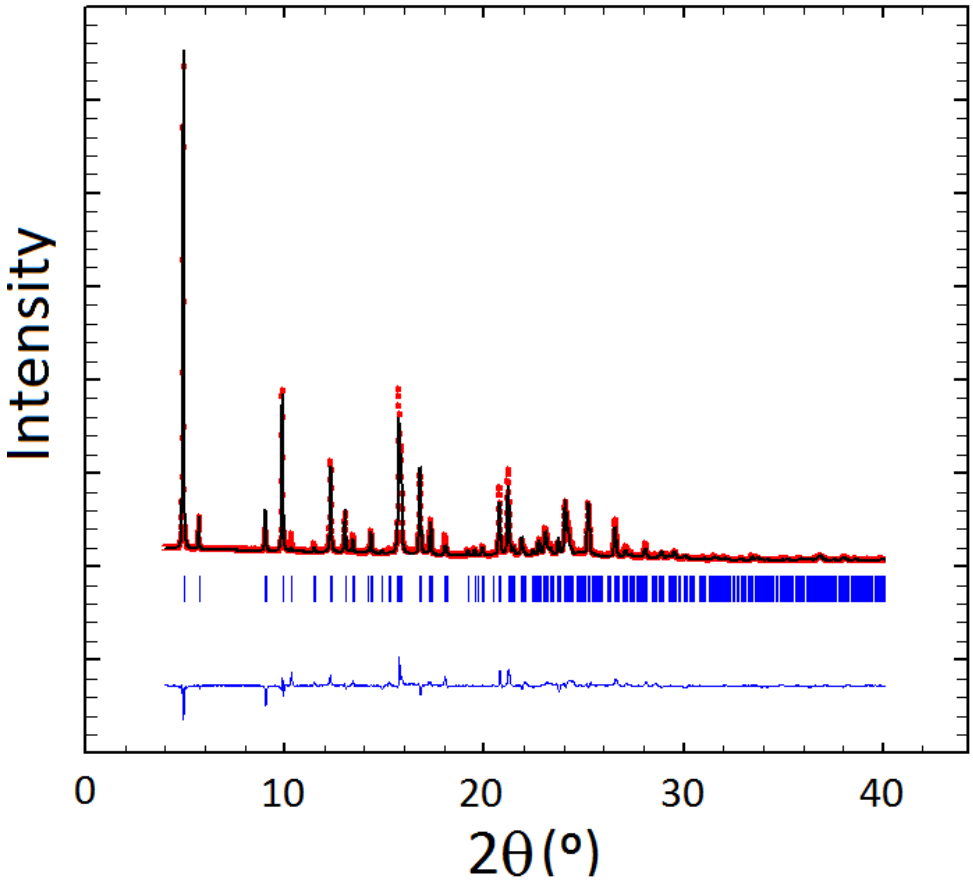

Fig. 2. Final Rietveld plot for the crystal structure refinement of Sildenafil form II. Agreement factors: Rwp = 12.3%, Chi^2 = 4.93. The plot shows the experimental powder XRD profile (red marks), the calculated powder XRD profile (black solid line), and the difference profile (blue, lower line). Tick

marks indicate peak positions.

2.2.2 Differential Scanning Calorimetry (DSC). Differential scanning calorimetry analysis were carried out by means of a Mettler-Toledo DSC-822e calorimeter. Experimental conditions: aluminium crucibles of 40 μL volume, atmosphere of dry nitrogen with 50 mL/min flow rate, heating rate of 10°C/min. The calorimeter was calibrated with indium of 99.99% purity (m.p.: 156.4 ºC ΔH: 28.55 J/g).

2.2.3 Thermogravimetric Analysis (TGA). Thermogravimetric analyses were performed on a Mettler-Toledo TGA-851e thermobalance. Experimental conditions: alumina crucibles of 70 μL volume, atmosphere of dry nitrogen with 50 mL/min flow rate, heating rate of 10°C/min.

2.2.4 Dynamic Vapor Sorption (DVS). The water sorption and desorption processes were measured on a DVS-1000 instrument from Surface Measurement Systems. The samples were mounted on a balance and studied over a humidity range from 0% to 90% RH, and then decreased to 0% RH at 25 and 40°C using a three cycles method. The equilibrium condition for each step was set to a mass constancy of ± 0.001% over 60 minutes and a maximum time limit of 1440 min for each step.

3 RESULTS AND DISCUSSION

Sildenafil, the ingredient of Viagra, is the first oral drug used for the medical treatment of erectile dysfunction and has been recently used for the treatment of pulmonary hypertension[30, 31] but due to its low water solubility it is generally formulated as sildenafil citrate.[32] The crystal structures of sildenafil base, sildenafil citrate monohydrate and sildenafil saccharinate have been reported elsewhere.[29] With the aim to study the solid state of this API we have conducted an extensive polymorph screening by using a broad set of thermodynamic and kinetic experimental conditions from a variety of 54 solvents[33] which produced 98 individual crystalline solids. Six new solvates (toluene, anisole, acetonitrile, propanenitrile, dioxane and chloroform) and a new polymorph of Sildenafil have been discovered and their crystal

structures solved. The DFT analysis of toluene, anisole, dioxane and chloroform solvates are the subject of another research paper, in which the formation of an apparently innocent intramolecular H-bond has a remarkable influence on the solid state architecture of the sildenafil solvates.[34]

During the polymorph screening with 53 out of 54 organic solvents only the known form I or new solvates (as mentioned before) were obtained except when acetonitrile was used. In particular, crystallizing or slurrying in this solvent produced three new solid forms depending on whether the solid obtained was extensively dried or not. When the solid obtained by slurrying sildenafil in acetonitrile was dried under vacuum an anhydrous new form (Form II) was obtained but if the solid was only filtered and directly analyzed without further drying a new solvate (form ACN_{II}) was produced with 2:1 sildenafil:acetonitrile stoichiometry (deduced from TGA analysis, figure S10). Moreover, needles of a different acetonitrile solvate with 1:1 sildenafil:acetonitrile stoichiometry were obtained (solvate form ACN_{I}) by slow evaporation of an acetonitrile solution of sildenafil at room temperature and its crystal structure solved by SXRD analysis. The PXRD diffractogram of solvate form ACN_{II} was indexed (Figure S13) at room temperature and its stoichiometry deduced from TGA analysis (Figure S10). The two solvates show a very similar PXRD diagram and cell parameters, which suggests that both solvates can be isostructural, Fig 3. See ESI† for further detail.

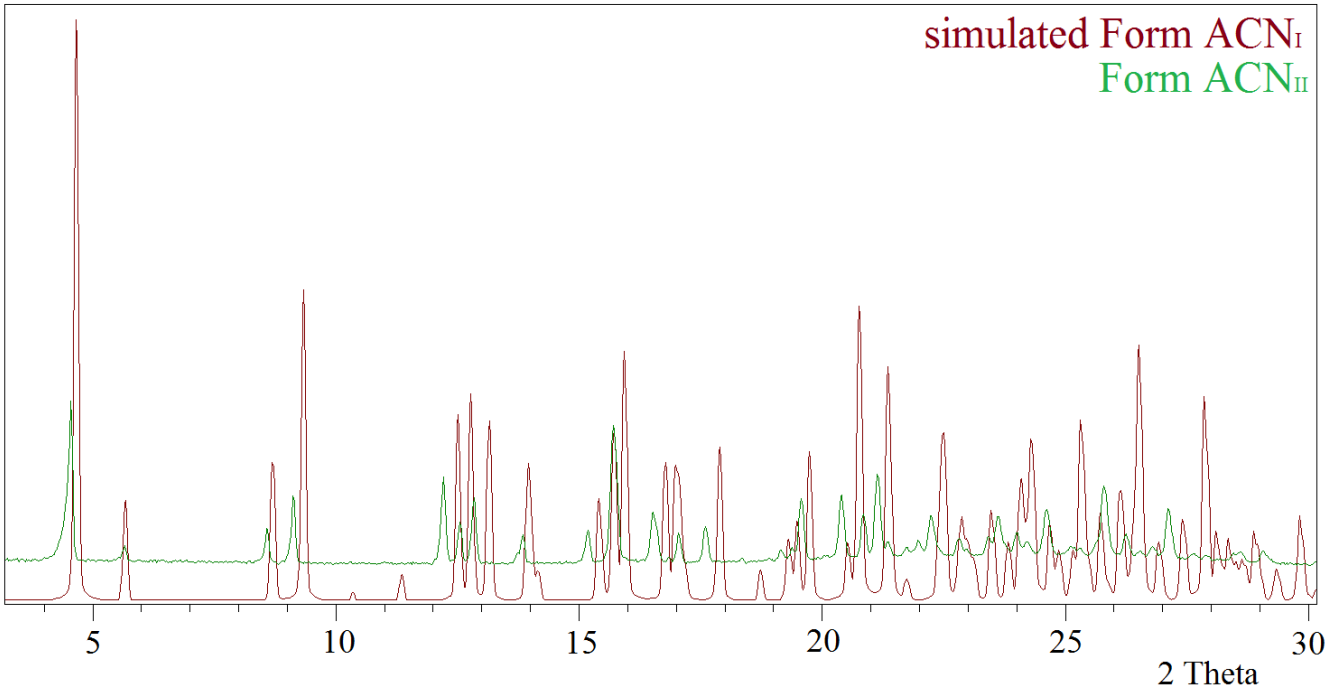

Fig. 3 PXRD diagrams of acetonitrile solvates form I (simulated from crystal structure) and II

The DSC of Sildenafil form II shows two overlapped endothermic/exothermic phenomena prior to the melting of form I (Fig. 4) while modulated DSC (Fig. S8 ESI†) shows in the reversing signal an increase of heat capacity without melting followed by an exothermic broad peak in the non-reversing signal, suggesting that form II transforms into form I upon heating through a two-steps process involving a glass-like solid. On the other hand, desolvation of solvate form ACN_{II} by air drying at room temperature produced the new anhydrous form II while DSC of solvate form ACN_{II} showed a melting point which is 5°C lower than form I, probably due to lower crystallinity of the sample after desolvation and recrystallization (Figures 4, S9 and S10).

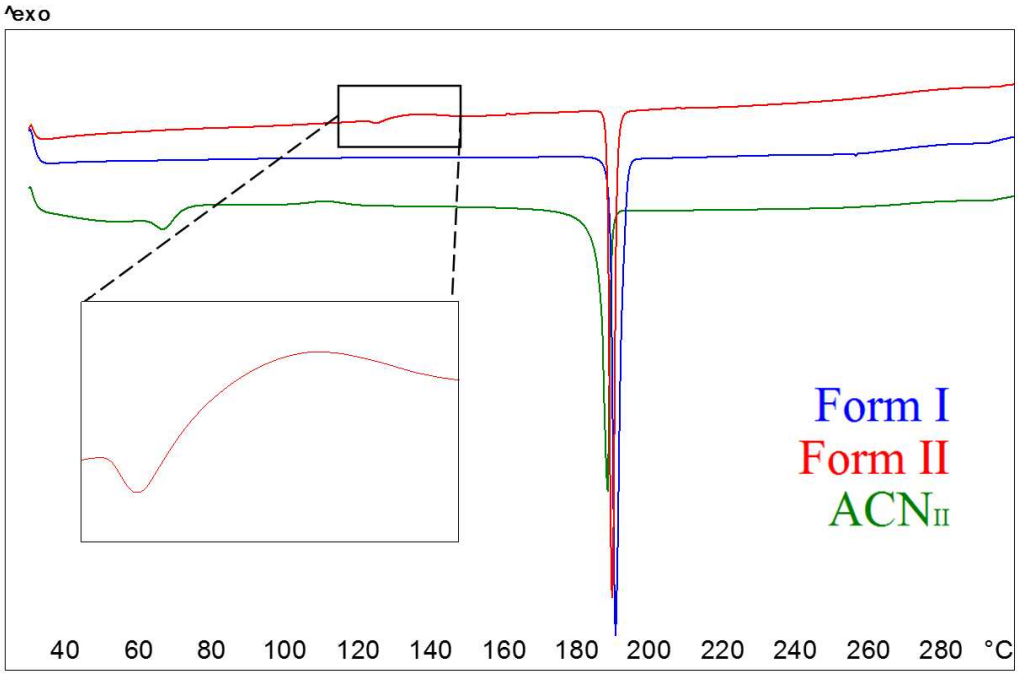

Fig. 4 DSC thermograms of anhydrous forms I (m.p. onset: 189 ºC; enthalpy: 87.1 J/g) and II (m.p. onset: 188 ºC; enthalpy: 92.4 J/g) and solvate form ACN_{II} (m.p. onset: 184 ºC; enthalpy: 75.6 J/g) of Sildenafil

The crystal structure of the new anhydrous form II was solved by means of direct space strategies from PXRD data and the analysis of the crystal structures reveals that anhydrous form II is an isomorphic desolvate of the new acetonitrile solvate form ACN_I. Fig. 5 shows that the only significant difference between both forms is the more opened conformation of the propyl groups in the desolvate which cannot completely fill the voids left by the removed solvent.

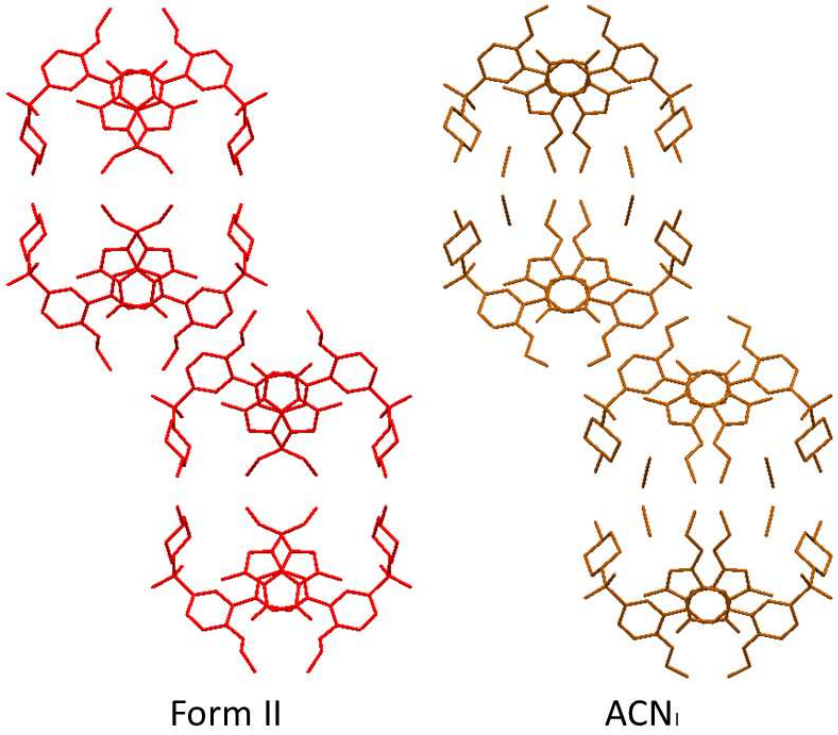

Fig. 5 Crystal structures of anhydrous form II and ACN solvate form ACN_I

The fact that anhydrous form II has only been detected in one out of 54 solvents can explain why new anhydrous form II has not been previously reported in literature and points out an important conclusion of this work as it will be discussed later.

The crystal structures of the two anhydrous forms at room temperature have been compared and a careful analysis of the packing reveals that the assymetric unit independent molecules of both forms establish the same strong intramolecular hydrogen bond between the ethoxy oxygen and the pyrimidine nitrogen. Thus, the observed differences can be considered as conformational adjustments of the same gas-phase conformer, according to the cutoff value proposed by Cruz-Cabeza and Bernstein in their analysis of conformational polymorphism[35] since the RMSD value computed using Mercury is less than 0.375 Å. Among the observable conformational adjustments the most relevant one involves the propyl groups, Fig. 6.

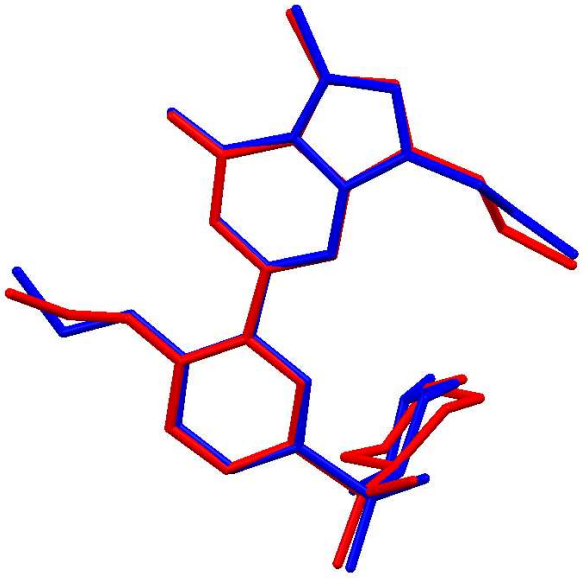

Fig. 6 Overlap of sildenafil molecules of anhydrous forms I (blue) and II (red). The computed root-mean-square distance (RMSD) is 0.338 Å

This can be better visualized through the fingerprint plots[36, 37] from Hirshfeld surfaces.[38] Although the essential features of the intermolecular atom-atom contacts are very similar, in form II the H···H contacts (highlighted with a black circle in Fig. 7) are much shorter than in form I as a consequence of the necessary folding of the propyl groups to maintain free the cavity previously occupied by the acetonitrile molecules in the solvate. In acetonitrile solvate ACN_I the short H···H contacts were already present and while anhydrous form I has a more extended configuration with less short H···H contacts the desolvate form II keeps much of the parent structure of ACN_I solvate, which explains why the short H···H contacts are also present in form II (see table 1 and 2 of ESI). These interatomic contacts are presumably repulsive according to the accepted van der Waals diameter of the hydrogen atom (1.1-1.2 Å). However only a small number of organic crystal structures have been reported with H···H interatomic distances lower than 2.2 Å,[39] which are associated with repulsive forces to preserve the internal equilibrium in the crystal structure,[40] as appears to be the case of anhydrous form II and solvate form ACN_I. See ESI† for further detail.

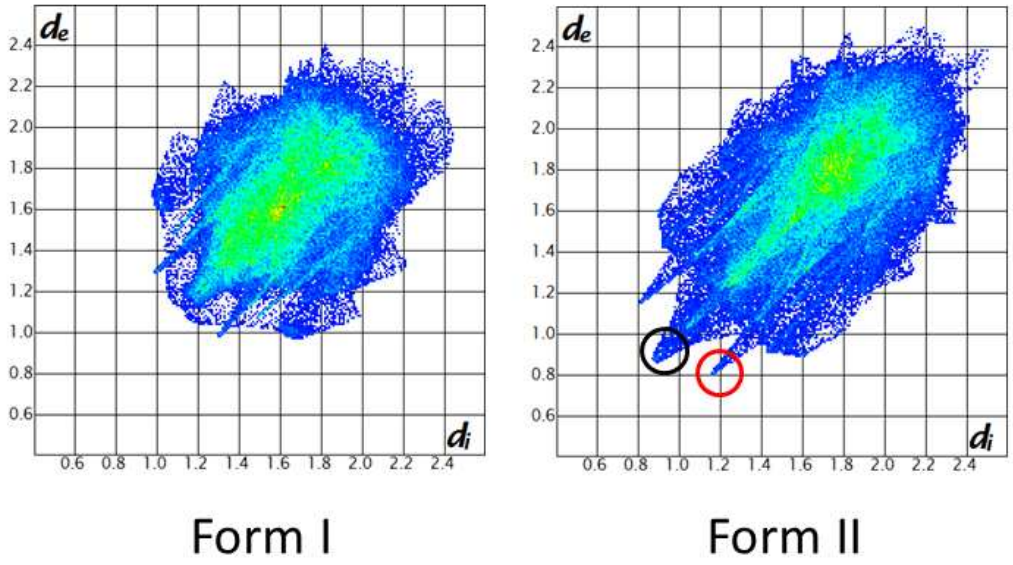

Fig. 7 Fingerprint plots computed from Hirshfeld surfaces of form I (left) and form II (right). Strong H···O contacts are highlighted in red and H···H contacts in black.

The most important consequence of anhydrous form II being an isomorphic desolvate of acetonitrile solvate is that there are bigger finite voids (rather than interconnected channels) than in form I. These have been calculated using the contact surface model using Mercury with a probe of 0,88 Å radius and shown in Fig. 8. Since crystal structures of anhydrous form I and solvate ACN_I have been solved at room temperature there is disorder on the propyl groups (not present at 100 K, data not shown), which can be explained based on the fact that propyl groups do not stablish strong intermolecular interactions with the surrounding atoms. This disorder is also probably present in anhydrous form II because the voids are bigger, however since the structure has been solved by direct space methods from PXRD the disorder cannot be directly measured.

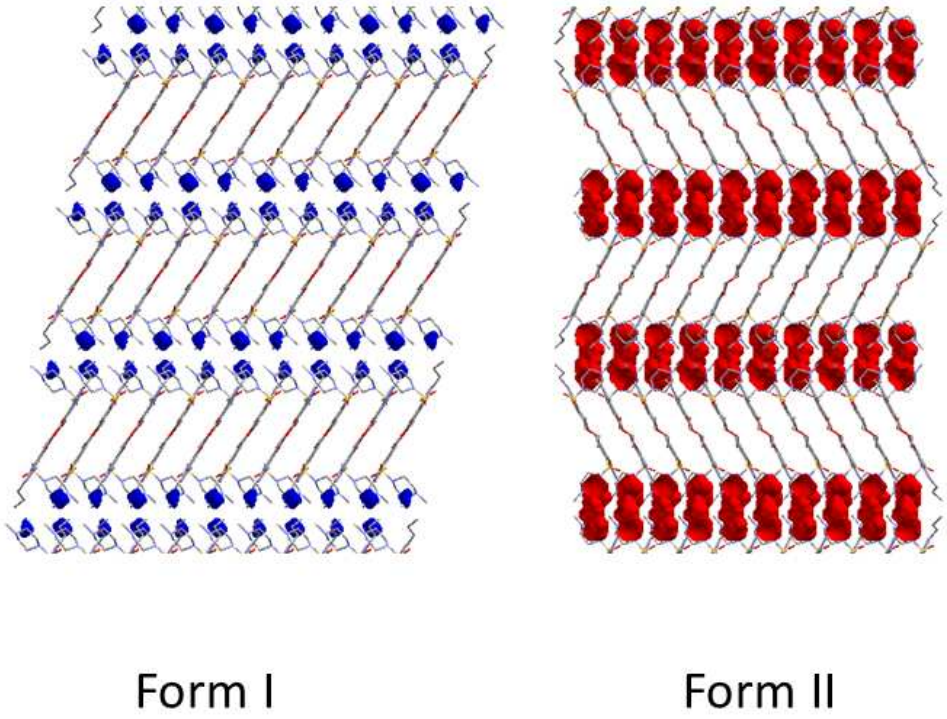

Fig. 8 Calculated voids of anhydrous forms of Sildenafil

On the other hand, the intermolecular contacts in both forms are very similar with hydrogen-bonded zig-zag chains formed between the carbonylic oxygen and the aromatic protons. Moreover, the same self-assembled dimers are formed through weak hydrogen bonds between the sulphoxide oxygens and ethyl groups and finally the same stacked configuration between aromatic rings are also observed. However, an important packing difference is present as a consequence of a non-crystallographic inversion center in one of every three layers (highlighted in Fig. 9) in form II with respect to form I. Thus, forms I and II can be considered morphotropic polymorphs since a non-crystallographic rearrangement transforms one form into the other.[41]

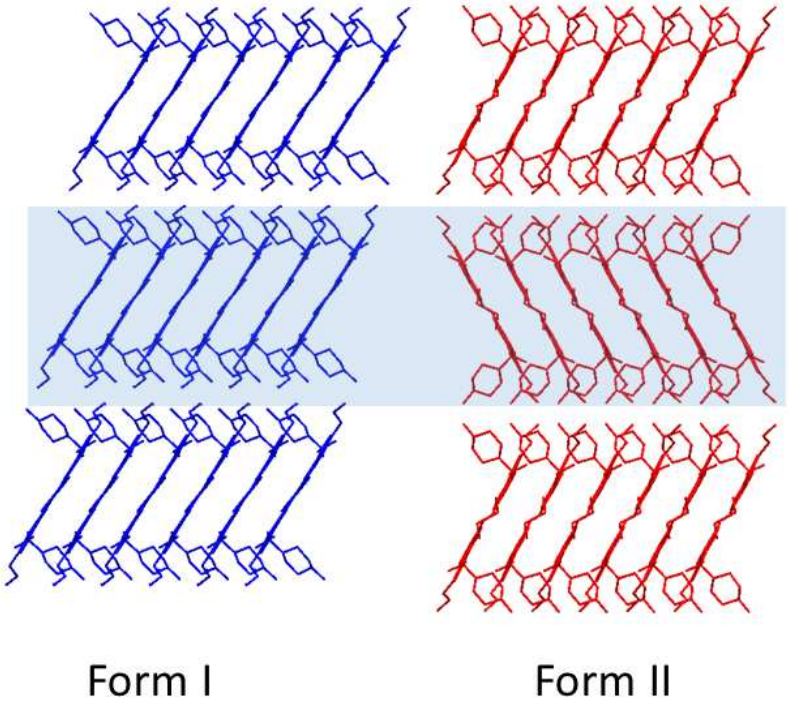

Fig. 9 Packing in the b axis direction showing the layer involved in a non-crystallographic inversion center

In spite of the considerable research conducted with solvated drugs the mechanisms that explain the solvate formation are still unclear. However, two different mechanisms (or a combination of both) in which solvent molecules incorporate into the crystal lattice have been postulated: solvent molecules can provide extra intermolecular interactions (a) and/or they help to decrease voids in the crystal (b).[42] In order to assess the stability of the less dense anhydrous form II, the potential to absorb water and acetonitrile of both anhydrous forms has been tested. DVS experiments have been performed and they show that form I only absorbs 0.23 and 0.73 % moisture at 25°C and 40°C respectively while form II absorbs 4.64 and 1.36 % moisture at 25°C (Fig. 10) and 40°C respectively (See ESI† for further detail). The fact that form II absorbs more water than form I when exposed to high relative humidity can be due to the presence of bigger voids in form II that attracts more water by capillary condensation. The formation of new hydrates has not been detected by PXRD analysis of the resulting samples after the

DVS experiments. Moreover, a low percentage of form I was detected in the sample which was initially form II, which suggests a water-assisted phase transition, as has been shown for paracetamol.[43]

On the other hand, when exposed to acetonitrile vapours both anhydrous forms convert into solvate form ACN_{II} but not to solvate form ACN_{I}, which suggests that the 1:1 acetonitrile solvate is formed through a dissolution/recrystallization process while the 2:1 acetonitrile solvate is formed by solvent diffusion.

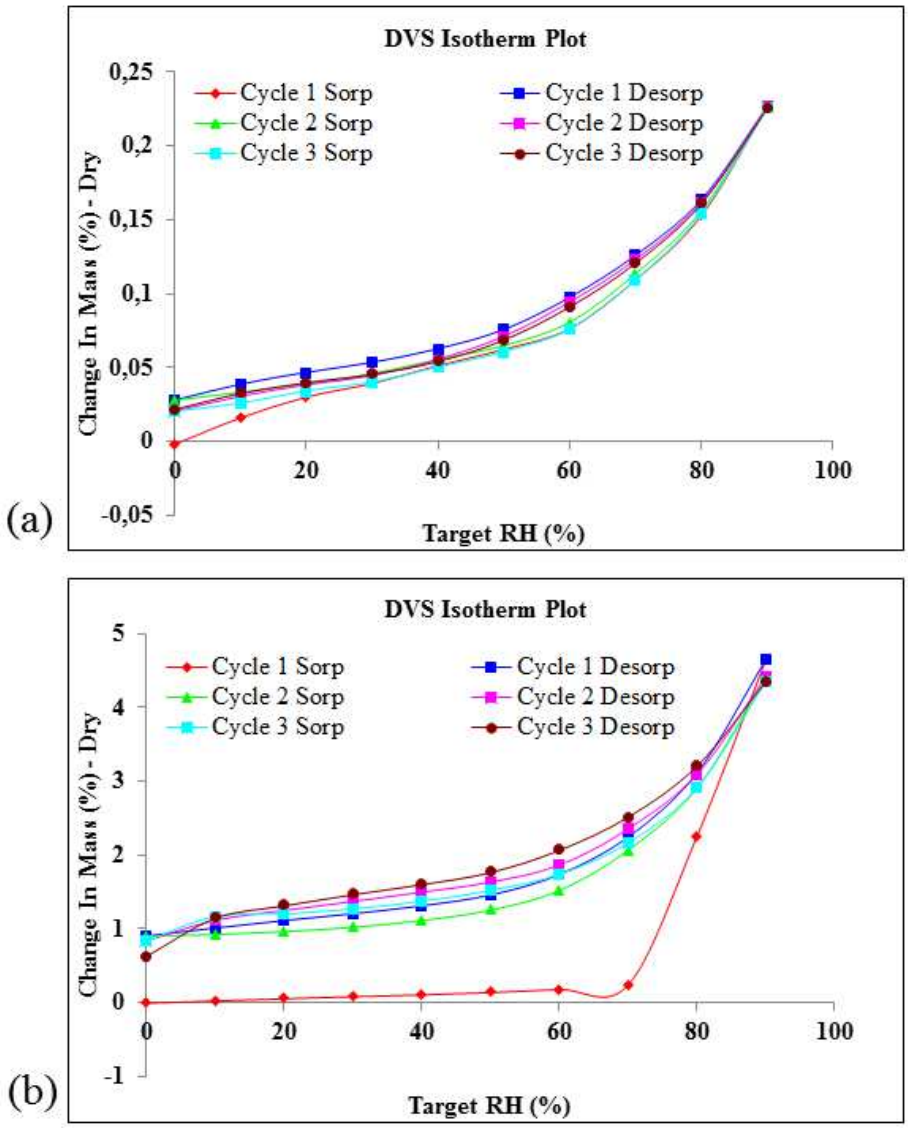

Fig. 10 Dynamic vapour sorption isotherms of form I (a) and form II (b) at 25°C

Finally, a new propanenitrile solvate was discovered during the solid forms screening. Interestingly, although acetonitrile and propanenitrile only differ in one methylene group the crystal structures of both

solvates are dramatically different, with the structure of the propanenitrile solvate resembling that of anhydrous form I. (Fig. 11). Desolvation under vacuum of the propanenitrile solvate produced anhydrous form I, an expected outcome due to the packing similarity between both forms.

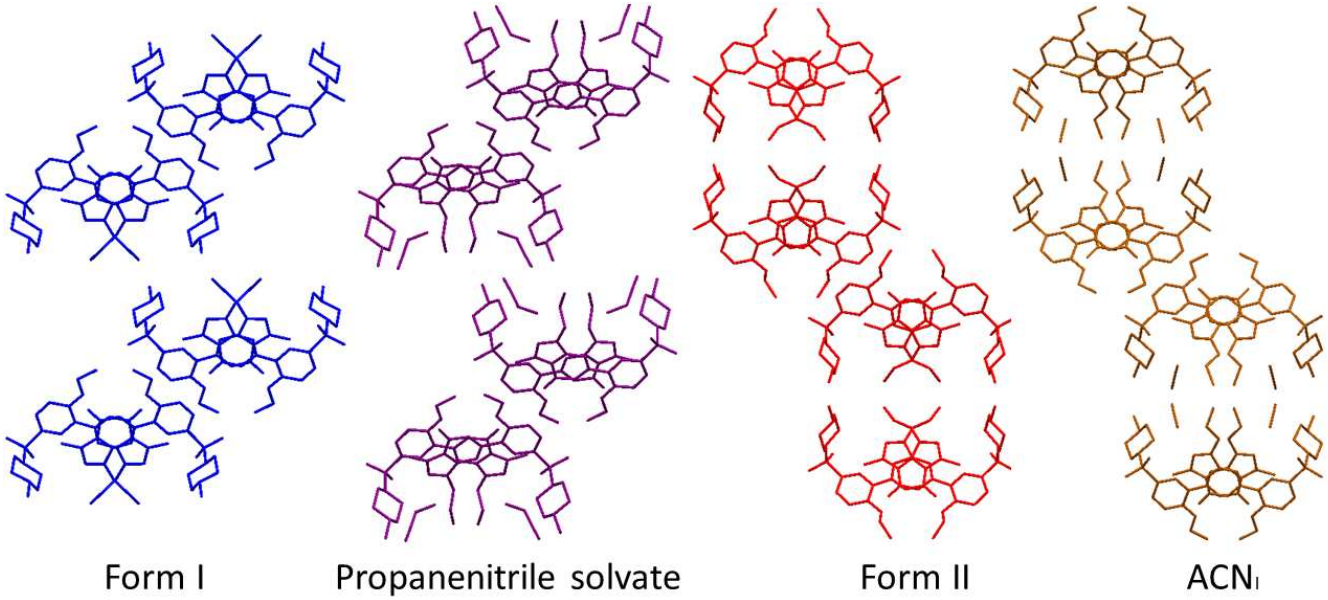

Fig. 11 Crystal structures of anhydrous form I, propanenitrile solvate, anhydrous form II and acetonitrile solvate form ACN_I

4. CONCLUSIONS

In summary, we have discovered a new anhydrous form of Sildenafil (form II) which is a desolvate of a new 1:1 acetonitrile solvate. Both anydrous forms are morphotropically related and the presence of voids in form II are created by desolvation of the acetonitrile solvate. Although 54 organic solvents have been tested during the solid forms screening the new polymorph is only obtained when acetonitrile is used. Thus, this study highlights the importance of intensive solvate screening during early stages of a polymorph/cocrystal screen of Active Principle Ingredients because some solvates can be precursors and provide the key to the discovery of potential metastable polymorphs that otherwise would remain unknown.

5. SUPPORTING INFORMATION

DSC, TGA, DVS curves of anhydrous forms and acetonitrile solvate. Hirshfeld analysis of anhydrous forms. Cell indexation of ACN solvate form II This material is available free of charge via the Internet at http://pubs.acs.org

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Polymorphism of Sildenafil: A new metastable desolvate

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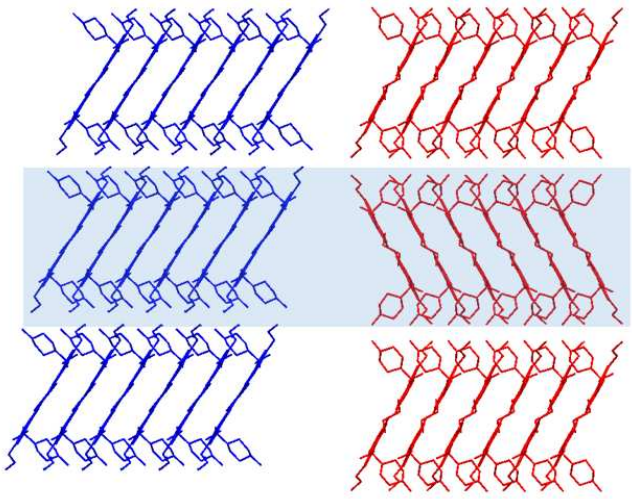

SYNOPSIS TOC. A new anhydrous polymorph of the free base of sildenafil and two solvates (acetonitrile and propanenitrile) have been discovered and fully characterized. The new polymorph can be considered a desolvate of the acetonitrile solvate and is related to the most stable form I by morphotropism. The new polymorph can only be obtained by desolvation of the acetonitrile solvate. Thus, this study is a new example of the importance of this multicomponent family of solid forms in the discovery of new polymorphs of Active Pharmaceutical Ingredients.