Combined Virtual/Experimental Multicomponent Solid Forms Screening of Sildenafil: New Salts, Cocrystals, and Hybrid Salt–Cocrystals

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ABSTRACT:

New multicomponent solid forms of sildenafil have been discovered by means of a combined virtual/experimental cocrystal screening. Coformer selection of candidates was conducted based on an in silico screening method from a database of more than 2000 organic compounds, and the intensive experimental screen produced 23 new solid forms. Since the 12 coformers chosen have a combination of phenol and carboxylic acid groups, a variety of cocrystals, salts, and hybrid salt-cocrystals were discovered and characterized.
1. INTRODUCTION

Cocrystals of active pharmaceutical ingredients (APIs) have received massive attention over the past decade because they offer many opportunities to improve physicochemical properties of drugs. Indeed, solubility is one of the most important properties for a drug compound since it has a direct impact on bioavailability, and the cocrystal approach is a versatile toolbox to tune this and another important property such as stability because of the high number of available potential coformers.

On February 2018, the Food and Drug Administration (FDA) released a final guidance titled “Regulatory Classification of Pharmaceutical Co-Crystals Guidance for Industry”, providing applicants planning to submit new drug applications with information on the regulatory classification of pharmaceutical cocrystals, classifying them as a new form of the API, comparable in that respect to polymorphs, hydrates, salts, etc. The FDA asks the applicants to provide evidence to demonstrate that “both the API and coformers are present in the unit cell” and “the component API and coformer co-exist in the cocrystal which interact nonionically”. The FDA guidance suggests that the applicant consider the difference of ΔpKa between the API and the coformer or to provide evidence that proton transfer has not occurred in the lattice by means of spectroscopic tools or other orthogonal approaches. Thus, from a regulatory point of view, it is very important to assess the proton transfer in a multicomponent process.

Sildenafil, the active principle of Viagra, is the first oral drug used for the medical treatment of erectile dysfunction in elderly patients, and it was initially used as an antihypertensive drug but due to its poor aqueous solubility and low bioavailability it is generally formulated as sildenafil citrate. This solid form still exhibits moderate bioavailability, and this is the reason why some efforts have been conducted to discover new salts and cocrystals with enhanced physicochemical properties. In this sense, a sildenafil/acetylsalicylic cocrystal exhibiting enhanced intrinsic dissolution rate compared to sildenafil citrate has been reported. Moreover, pharmacokinetics of salts and cocrystals of sildenafil with dicarboxylic acids has been studied, and the glutarate salt was revealed to be a good candidate for alternative formulation of the citrate salt. The crystal structures of sildenafil base, sildenafil citrate monohydrate, sildenafil saccharinate, and sildenafil acesulfamate have been published in the literature, and some of us have described a polymorph of sildenafil free base and new solvates. With the aim to discover new multicomponent forms and extend the solid state knowledge of this important API, we have conducted a combined virtual/experimental salt/cocrystal screening by using a broad set of thermodynamic and kinetic experimental conditions. Twenty-three new solid forms of sildenafil, including salts, cocrystals, and hybrid salt–cocrystals, have been discovered and some of their crystal structures solved.
2. MATERIALS AND METHODS

2.1. Materials. Sildenafil (SIL) used in this study was of reagent grade and used as received from Polpharma (form I). The coformers quercetin (QUE), methyl gallate (MEG), tartaric acid (TAR), 3-hydroxybenzoic acid (3-HBA), 4-hydroxybenzoic acid (4-HBA), resorcinol (RES), 3,4-dihydroxybenzoic acid (3,4-DHBA), and caffeic acid (CAF) were purchased from Sigma-Aldrich.

2.2. Methods. 2.2.1. Virtual Cocrystal Screening. For each compound, the molecule was drawn in an extended conformation and energy minimized using the molecular mechanics methods implemented in Torchlite.17 Gaussian 09 was used to optimize the geometry and calculate the MEPS on the 0.002 Bohr Å−3 electron density isosurface using density functional theory (DFT) and a B3LYP/6-31G* basis set.18 The MEPS was converted into SSIPs using in-house software.19

2.2.2. Cocrystal Screening. Screening through liquid assisted grinding experiments (LAG) was conducted by preparing a saturated solution of the most soluble component (SIL or coformer) in different solvents in a sealed vial under stirring. A small quantity of the less soluble component was added until it did not dissolve anymore. The suspension was stirred at different times, and the resulting solids were filtered and analyzed by PXRD. Screening through reaction crystallization (RC) was conducted by preparing suspensions of SIL and coformer in different molar ratios (40–1200mg of the final mixture) in selected solvents. The sealed vials were stirred for different times, and the resulting solids were filtered and analyzed by PXRD.

2.2.3. Solution Crystallization. Solutions of SIL/coformer in a 1:1 molar ratio (10–20 mg of the final mixture) were prepared in different solvents and heated in a heating stainless steel block. The heater was switched off, and the solutions were allowed to slowly cool down to 25°C inside the heating block. The samples which did not crystallize were tightly sealed and kept at 25°C until precipitation was observed.

2.2.4. Synthesis of the Different Crystal Forms of Sildenafil. Details of synthesis and characterization of each form can be found in Supporting Information (see section 1 and Table S1). Stoichiometry has been assessed based on NMR and thermogravimetric analysis (TGA) measurements when the crystal structure is not available. In those cases where the crystal structure has not been solved, the definition of the form as a salt or a cocrystal has been done based on the probability of proton transfer determined with eq 3.

Twenty-three multicomponent forms of SIL (cocrystals, salts, and hybrid salt−cocrystal) have been obtained through a cocrystal screening with 8 out of the 12 coformers used. Five cocrystal forms of SIL have been obtained with three coformers: two forms with quercetin in a 1:1 stoichiometry (one as an isopropylol solvate, SIL-QUE I, and one as a tetrahydrofuran solvate, SIL-QUE II); two with resorcinol in two different stoichiometries (one in a 1:1 molar ratio, SIL-RES I, and one in a 1:2 molar ratio, SIL-RES II); one form with methyl gallate in a 1:1 stoichiometry, SIL-MEG. Fourteen salts of SIL have been obtained with five coformers: one form with 3,4-dihydroxybenzoic acid in a 1:1 stoichiometry as an isopropylol solvate, SIL-3,4-DHBA I; four forms with tartaric acid in two different stoichiometries: two in a 1:1 molar ratio (an anhydrous form, SIL-TAR I, and an isopropylol solvate, SIL-TAR III); two in a 2:1 molar ratio (an anhydrous form, SIL-TAR II, and an isopropylol solvate, SIL-TAR IV); two forms with caffeic acid in a 2:3 stoichiometry (one as an anhydrous form, SIL-CAF I, and one as a monohydrate, SIL-CAF II); three forms with 3-hydroxybenzoic acid in a 1:1 stoichiometry (one as an acetonitrile solvate, SIL-3-HBA I, one as a tetrahydrofuran solvate sesquihydrate, SIL-3-HBA II, and one as an anhydrous form, SIL-3-HBA III); four forms with 4-hydroxybenzoic acid in a 1:1 stoichiometry (two as anhydrous forms, SIL-4-HBA I and SIL-4-HBA III, one as a hemiisopropanol solvate, SIL-4-HBA II, and one as a tetrahydrofuran solvate, SIL-4-HBA IV). Four hybrid salt−cocrystal forms of SIL have been obtained with two coformers: three forms with 3,4-dihydroxybenzoic acid in two different stoichiometries (two of them in a 1:2 molar ratio as acetonitrile solvates, SIL-3,4-DHBA II...
and SIL-3,4-DHBA III, and one in a 2:3 molar ratio as a dehydrate, SIL-3,4-DHBA IV) and finally one form with 3-hydroxybenzoic acid in a 2:3 stoichiometry as a dehydrate, SIL-3-HBA IV.

2.2.5. X-ray Crystallographic Analysis. Single crystal X-ray diffraction intensity data of the different crystal forms of sildenafil 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 multiscan method (SADABS).20 The structures were solved and refined using the Bruker SHELXTL Software Package, a computer program for automatic solution of crystal structures and refined by fullmatrix least-squares method with ShelXle Version 4.8.0, a Qt graphical user interface for SHELXL computer program.21

Powder X-ray diffraction patterns were 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 40° in 20, with a step size of 0.026° or from 2 to 70° in 20, with a step size of 0.013° with measuring times of 30 min to 4 h. The powder diffractograms were indexed, and the lattice parameters were refined by means of LeBail fits by means of Dicvol04,22 and the space groups were determined from the systematic absences. A summary of crystal data and relevant refinement parameters are given in Tables 1 and 2.

2.2.6. 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 a 50 mL/min flow rate, and heating rate of 10 °C/min.

The calorimeter was calibrated with indium of 99.99% purity (m.p.: 156.4 °C, ΔH: 28.55 J/g).

2.2.7. 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, and a heating rate of 10 °C/min.

2.2.8. Nuclear Magnetic Resonance (NMR). Proton nuclear magnetic resonance (1H NMR) spectra was recorded on a Varian Mercury 400 (400 MHz). Chemical shifts for proton are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to residual proton in the NMR solvent (DMSO-d6: δ 2.50). Experimental conditions: delay: 1; pulse: 45°; scans: 32 or 64.

2.2.9. Dissolution Study. The dissolution measurements were carried out only with the solid forms that could be obtained pure in amounts sufficient to perform a dissolution study: pure sildenafil, salts of sildenafil with citric acid, tartaric acid, 3-HBA and 3,4-DHBA, a cocrystals with RES, QUE, and two hybrid salt-cocrystals of sildenafil with 3,4-DHBA. The dissolution was determined in 0.1 N HCl (pH 1.2), phosphate buffer pH 6.5, and a biorelevant dissolution medium fasted state simulated intestinal fluid (FaSSIF) at 25 °C. For dissolution studies 40 mg of crystalline compounds were added to the dissolution medium stirred at 100 rpm over 24 h, and samples were withdrawn at 1 and 24 h. The amount of SIL dissolved in 1 h (D1h) and 24 h (D24h) was determined using the HPLC technique. The details about dissolution medium and HPLC method are provided in Supporting Information.
3. RESULTS AND DISCUSSION

3.1. Virtual Cocrystal Screen. We selected the coformers for experimental screening based on the virtual cocrystal screening methodology developed by some of us to predict the probability of cocrystal formation. This computational tool has been validated using experimental data extracted from the literature.

The difference between the calculated energy of the cocrystal and the pure components was used to rank potential coformers. This approach uses surface site interaction points (SSIPs) calculated from the ab initio molecular electrostatic potential surface (MEPS) of the isolated molecule in the gas phase. The interaction of a molecule with its environment is described by a discrete set of SSIPs, each represented by an interaction parameter, $\varepsilon_i$, which is positive for a H-bond donor site (or positive region on the MEPS) and negative for a H-bond acceptor site (or negative region on the MEPS). The energy of interaction between two SSIPs, $i$ and $j$, is given by the product $\varepsilon_i \varepsilon_j$. We assume that pairwise interactions between SSIPs are optimized in a solid, and this provides a method for evaluating the interaction site pairing energy of a solid without knowledge of the crystal structure. The most positive SSIP is paired with the most negative SSIP, the next most positive SSIP with the next most negative, and so on, giving a hierarchical list of interactions. This interaction site pairing strategy provides a straightforward method for estimating the energy of a solid, $E$ (eq 1). The same approach can be used to estimate the energy of a cocrystal, and the difference between the interaction site pairing energies of the cocrystal and the pure components, $\Delta E$, can be used to estimate the probability of cocrystal formation (eq 2).

\[
E = \sum \varepsilon_i \varepsilon_j \quad (1)
\]

\[
\Delta E = -(E_{\text{cocrystal}} - E_1 - E_2) \quad (2)
\]

where $E_1$, $E_2$, and $E_{\text{cocrystal}}$ are the interaction site pairing energies of the pure solids, 1 and 2, and a 1:1 cocrystal respectively. Note that this definition means that $\Delta E$ is always positive, and a large value indicates a high probability of cocrystal formation.

Some of us have previously applied the method to successfully predict the formation of new cocrystals, and in this work we have followed this theoretical approach to guide the selection of a limited number of coformers to test experimentally. Thus, the difference between the interaction site pairing energies of the 1:1 cocrystal and the pure components was calculated for each sildenafil/coformer combination using a coformer database which contains more than 2000 organic compounds (including 860 products from the GRAS list). The coformers were ranked in order of decreasing $\Delta E$, and only 12 coformers were chosen from the top 100 compounds according to toxicity criteria and probability of success in a cocrystallization experiment (Table 3). This theoretical approach
defines an energy threshold of 11 kJ/mol where the probability of cocrystal formation is higher than 50%. Thus, only coformers with ΔE > 11 kJ/mol were chosen for experimental screening.

Since sildenafil has a strong basic group, the formation of salts with strong carboxylic acids is expected. In fact, the formation of a salt or a cocrystal can be assessed based on the “rule of thumb”31 which states that salts are formed when ΔpKa [pKa(base) − pKa(acid)] ≥ 3, and a cocrystal is expected when this value is ≤0, the combinations with a value 0 ≤ [pKa(base) − pKa(acid)] ≤ 3 being much less reliable and falling around a “salt-cocrystal continuum” region.32 This uncertainty motivated the analysis and correlation by Cruz-Cabeza33 of a big set of experimental cocrystal/salt data in order to develop a more reliable equation to predict the salt/cocrystal outcome. According to this statistical analysis, eq 3 allows prediction of the probability of proton transfer around the region of ΔpKa values between −1 and 4.

\[
P(\%) = 17ΔpKa + 28 \quad (3)
\]

Sildenafil has a basic functional group (piperazine) with a pKa value of 6.78,34 and we have applied this statistical approach to the coformers with acidic groups selected from the virtual cocrystal screening to assess the probability of salt formation (Table 4). Coformers with acidic groups such as (3-hydroxybenzoic acid, 4-hydroxybenzoic acid, caffeic acid, 3,4-dihydroxybenzoic acid, and tartaric acid) were expected to form salts. However, salt stoichiometry is an important outcome not always easy to predict because hybrid salt–cocrystal forms are also possible. In this sense, there are interesting examples in the literature with unexpected stoichiometries due to the presence of nonionized molecules in the crystal structure such as the p-coumaric acid/quinine39 or the trans-N,N’-dibenzyl diamino cyclohexane/2,3-dichlorophenylacetic acid40 hybrid salt–cocrystals. Moreover, Aakeröy et al.41 suggested in a structural analysis of more than 80 cocrystals and salts formed between carboxylic acids and Nheterocycles that the formation of unexpected hybrid salt–cocrystals could be because carboxylate moieties are not readily satisfied by a single hydrogen-bond donor making necessary the presence of neutral carboxylic acids in the crystal structure. We have examined the Cambridge Structural Database (version 5.39, 2018) in order to assess the formation of hybrid salt–cocrystal forms in multicomponent crystals containing a piperazine ring (the basic group of sildenafil) and a carboxylic acid (Figure 3).

A total of 247 crystal structures containing atomic coordinates were found and classified as salt, cocrystal, or hybrid salt–cocrystal according to the C–O bond lengths of the carboxylate moiety. Although 184 structures showed total proton transfer between donor and acceptor, 63 of them revealed that cocrystals or mixed salt-cocrystals were formed. This encouraged us to test the carboxylic acids previously chosen in the virtual cocrystal prediction. Table 5 summarizes the results of this structural analysis.

**3.2. Salt/Cocrystal Screening.** With the aim to discover new salts or cocrystals of sildenafil, an extensive multicomponent solid forms screening was conducted by using a broad set of thermodynamic
and kinetic experimental conditions from a variety of 54 solvents, which produced 194 individual crystalline solids (see Supporting Information for experimental and characterization details).

3.3. Crystal Structures Analysis. The crystal structures of 5 out of the new 23 forms of sildenafil have been solved by single crystal X-ray diffraction, and the following analysis shows that in all cases salts or hybrid salt-cocrystals have been formed with tartaric acid, 3-hydroxybenzoic acid, and 3,4-dihydroxybenzoic acid.

3.3.1. Tartaric Acid Salt Isopropanol Hemisolvate (SIL-TAR IV). Tartaric acid salt isopropanol hemisolvate crystallizes with one molecule of sildenafil cation, half molecule of tartrate dianion, and half disordered molecule of isopropanol in the asymmetric unit. Transfer of both protons of tartaric acid has been deduced since tartrate C–O distances are 1.183(9) and 1.232(8) Å. The dianion, which shows disorder between two conformations (in a 1:1 ratio), is encapsulated between two molecules of sildenafil establishing strong charge-assisted hydrogen bonds. Sildenafil/tartrate cages are packed with a combination of electrostatic interactions between sulphonamide moieties in a self-association fashion and weak hydrogen bonds between N-methylpyrazole rings (Figures 4 and 5). Molecular cavities are present and occupied by disordered molecules of isopropanol.

3.3.2. Hybrid 3-Hydroxybenzoic Acid Salt–Cocrystal Monohydrate (SIL-3-HBA IV). The hybrid salt–cocrystal formed by 3-hydroxybenzoic acid and sildenafil crystallizes with one molecule of sildenafil cation, one molecule of the carboxylate, half molecule of the carboxylic acid, and one molecule of water in the asymmetric unit. Chains of self-assembled sildenafil cations are formed through strong hydrogen bonds between the piperazinium ring and the carbonylic oxygen. As expected, strong charge-assisted hydrogen bonds are formed between the carboxylate anion and the piperazinium cation, but one molecule of the nonionized carboxylic acid interacts with the carboxylate anion via the phenol and carboxylic hydrogen in an alternate manner (Figure 9). Weak antiparallel dipole–dipole interactions between stacked pyrimidinone rings are established conferring extra stabilization to the crystal (Figure 8). In addition, one molecule of water is also present acting as a bridge between carboxylates (Figure 6).

3.3.3. 3-Hydroxybenzoic Acid Salt THF Hemisolvate Sesquihydrate (SIL-3-HBA II). The salt formed by 3-hydroxybenzoic acid and sildenafil crystallizes with one molecule of sildenafil cation, one molecule of the carboxylate, half disordered molecule of THF, and 1.5 molecules of water in the asymmetric unit. In spite of the different degree of proton transfer, this solid form is isostructural to the hybrid 3-hydroxybenzoic acid salt-cocrystal, and the same interactions between sildenafil and 3-hydroxybenzoate molecules are established. Moreover, identical channels are formed but filled by disordered tetrahydrofuran and water molecules instead of molecules of 3-hydroxybenzoic acid. Only small differences between both structures are present like, for instance, centroid–centroid distances measured between pyrimidinone rings and torsion angles of propyl groups (Figure 8).
3.3.4. Hybrid 3,4-Dihydroxybenzoic Acid Salt–Cocrystal Monohydrate (SIL-3,4-DHBA IV). The hybrid salt-cocrystal formed by 3,4-dihydroxybenzoic acid and sildenafil crystallizes with one molecule of sildenafil cations, one molecule of the carboxylate, half molecule of the carboxylic acid, and one molecule of water in the asymmetric unit. This solid form is isostructural to the hybrid 3-hydroxybenzoic acid salt–cocrystal. The presence of an extra phenol group in the 3,4-dihydroxybenzoic acid only reinforces the same packing without disrupting any of the main observed interactions in the hybrid 3-hydroxybenzoic acid salt–cocrystal. Figure 9 shows chains of carboxylate molecules linked by water molecules in both structures.

3.3.5. Hybrid 3,4-Dihydroxybenzoic Acid Salt–Cocrystal Acetonitrile Disolvate (SIL-3,4-DHBA II). The hybrid 3,4-dihydroxybenzoic acid salt–cocrystal acetonitrile disolvate crystallizes with one molecule of the sildenafil cation, one molecule of the carboxylate, one molecule of the carboxylic acid, and two molecules of acetonitrile in the asymmetric unit. In a similar way that the tartaric acid salt, instead of catemeric chains of sildenafil cations, self-assembled dimers are formed through charge-assisted hydrogen bonds (Figure 10).

However, the antiparallel dipole–dipole interactions between stacked pyrimidinone rings are not observed in this form. This is the only structure of this family of hybrid salts–cocrystals where water is not present, and this produces a different architecture of the coformer self-assembling, which consists of layers of alternate carboxylic/carboxylate interactions (Figure 11).

3.4. Dissolution Study. The dissolution studies were carried out at pH 1.2, pH 6.5, and FaSSIF (pH 6.5), which represent the average pH values of the fast state stomach and intestine, respectively. SIL has pH dependent solubility which decreases with an increase in pH. One of the major challenges in the dissolution study of multicomponent entities is continuous change in the solution composition due to precipitation of either of the component over the dissolution testing period. The solubility data generated may be erroneous due to limitations of the analytical method; for example, estimations carried out by UV spectrophotometry are subject to the overlap in the absorption spectra of the two components. We have used the HPLC method to quantify the amount of SIL dissolved; hence we see some difference in reported dissolutions compared to the previous SIL salt dissolution data reported.43 Figures 12, 13, and 14 (and Figures S75–S77 of the Supporting Information) show the dissolution data.

At pH 1.2 the amount dissolved from SIL salts was significantly higher than the cocrystals and the hybrid salt–cocrystal forms. The hybrid salt–cocrystals showed poor dissolution performance compared to cocrystals. The D1h and D24h values for SIL-TAR I were higher than for SIL-CIT, a commercially used salt of SIL. At pH 1.2 in the salt category SILTAR > SIL-3-HBA I > SIL-CIT > SIL-3,4-DHBA I. On the other hand D1h for SIL-RES II > SIL-QUE I and SIL-QUE II. As expected, the amount dissolved at pH 6.5 was at least 10 times lower than the amount dissolved at pH 1.2. But in both conditions, the amount of SIL dissolved was significantly higher for salts than for cocrystals and hybrid salt–cocrystals. Most of the cocrystals and hybrid salt–cocrystals did not provide any release of SIL at pH 6.5 or even in FaSSIF, which contains an additive like lecithin included in the dissolution media.
Thus, although an exhaustive solubility study of the new forms was not the main objective of this research, our data suggest that SILTAR could be a potential alternative (in terms of bioavailability) to the commercial citrate salt of sildenafil.
4. CONCLUSION

In summary, we have revisited the multicomponent solid form landscape of sildenafil by conducting a combined virtual and experimental screening. Twenty-three new solid forms have been discovered and characterized, and dissolution data have been measured for some of the solid forms suggesting the new tartrate salt as a potential alternative to the marketed citrate salt. The analysis of the five crystal structures solved by SXRD showed a variety of salts and hybrid salt–cocrystals with different hydrogen bond architectures and presence of solvent channels. This study extends the knowledge about the solid state of this important drug compound, contributes with new cases to the body of data of unexpected stoichiometric hybrid salt–cocrystals, and it is a new example of successful application of combined virtual/experimental methodologies for the discovery of new solid forms.
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Notes
The authors declare no competing financial interest.
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isopropyl acetate, diethylether, THF, 1-methyl-2-pyrrolidone, dimethyl ethylene glycol,
diisopropyl ether, dioxane, iodomethane, dichloromethane, 1,2-dichloroethane, chloroform, 1,1,1-
trichloroethane, 1,1,2-trichloroethane, formic acid, acetic acid, trifluoroacetic acid, propanoic
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Legends to figures

Figure. 1. Molecular structure of sildenafil.

Figure. 2 SSIPs calculated for sildenafil. Blue spheres correspond to Hbond donors and red spheres to H-bond acceptors.

Figure. 3 Fragments searched in multicomponent crystals in the CSD.

Figure. 4 Crystal structure of tartaric acid salt of sildenafil. The most relevant interactions are highlighted. Channels filled by solvent molecules are highlighted with gray circles.

Figure. 5 Sildenafil/tartrate cage in the crystal structure of tartaric acid salt of sildenafil.

Figure. 6 Chains of carboxylate/carboxylic acid molecules linked by molecules of water in the hybrid 3-hydroxybenzoic salt–cocrystal monohydrate.

Figure. 7 Representation of the crystal structures of 3-hydroxybenzoic acid salt and hybrid salt–cocrystal of sildenafil. The most relevant interactions have been highlighted, and hydrogens have been partially omitted for clarity. Channels filled by THF and water molecules in the salt or 3-hydroxybenzoic molecules in the hybrid salt–cocrystal are highlighted with gray circles.

Figure. 8 Antiparallel dipole–dipole interactions established between stacked pyrimidinone rings in the crystal structures of 3-hydroxybenzoic acid salt (right) and hybrid salt–cocrystal (left). Differences in centroid–centroid distances measured between pyrimidinone rings and torsion angles of propyl groups are shown for each structure.

Figure. 9 Chains of carboxylate molecules linked by molecules of water in the hybrid 3-hydroxybenzoic acid salt–cocrystal (left) and in the hybrid 3,4-dihydroxybenzoic acid salt–cocrystal (right).

Figure. 10 Crystal structure of 3,4-dihydroxybenzoic acid hybrid salt–cocrystal. Self-assembled dimers formed through charge-assisted hydrogen bonds are highlighted. Hydrogens have been partially omitted for clarity.

Figure. 11 Layers of alternate carboxylic (blue)/carboxylate (red) interactions.
Figure. 12 Comparative solubility of SIL salts, cocrystals, and hybrid salt–cocrystals in 0.1 N HCl (pH 1.2).

Figure. 13 Comparative solubility of SIL salts, cocrystals, and hybrid salt–cocrystals in phosphate buffer pH 6.5.

Figure. 14 Comparative solubility of SIL salts, cocrystals, and hybrid salt–cocrystals in FaSSIF.
FIGURE 3

\[
\begin{align*}
&\text{X} \\
&\text{N} \\
&\text{CH}_2 \\
&\text{N} \\
&\text{CH}_2 \\
&\text{X} \\
&\text{H}_2\text{C} \\
&\text{H}_2\text{C}
\end{align*}
\]

\[
\begin{align*}
&\text{O} \\
&\text{Y} \\
&\text{OH}
\end{align*}
\]
FIGURE 5.
FIGURE 8.
FIGURE 11.
FIGURE 13.

[Graph showing SIL concentration in ug/ml for various samples over 1hr and 24hrs]
FIGURE 14

[Graph showing SIL concentration in ug/ml for different compounds: SIL, SIL-citrate, SIL-TAR I, SIL-3-HBA I, SIL-RES II, SIL-QUE I, SIL-QUE II, SIL-3,4-DHBA I, SIL-3,4-DHBA III, SIL-3,4-DHBA IV. The x-axis represents different compounds and the y-axis represents concentration in ug/ml. The graph compares data at 1 hour and 24 hours (D1hr and D24hrs).]
Table 1 Crystal Data for the Different Crystal Forms of Sildenafil

| Structure  | SIL-TAR IV | SIL-3A-DHBA II | SIL-3A-DHBA IV | SIL-3HBA II | SIL-3HBA IV |
|------------|------------|----------------|----------------|-------------|-------------|
| Empirical Formula | C_{20}H_{26}N_{12}O_{10}S_{5} | C_{20}H_{28}N_{12}O_{10}S_{5} | C_{20}H_{28}N_{12}O_{10}S_{5} | C_{20}H_{28}N_{12}O_{10}S_{5} | C_{20}H_{28}N_{12}O_{10}S_{5} |
| Formula Weight | 115934 | 864.92 | 144754 | 675.77 | 139954 |
| Temperature (K) | 293(2) | 100(2) | 100(2) | 100(2) | 100(2) |
| Crystal System | tridymite | monoclinic | monoclinic | monoclinic | monoclinic |
| Space Group | P T | P21/n | P21/c | P21/n | P21/n |
| a, b, c (Å) | 6.3990(8) | 11.6418(8) | 17.6070(17) | 17.7205(18) | 17.5329(10) |
| α, β, γ (deg) | 90 | 102.749(3) | 117.101(5) | 102.748(3) | 105.591(2) |
| Volume (Å³) | 14097(3) | 4330.8(6) | 3398(7) | 3281.2(5) | 33565(3) |
| Z | 2 | 1.286 | 2.344 | 2.141 | 2.186 |
| Crystal size (mm²) | 6455.8/396 | 8875/0.370 | 7833/2.460 | 4567/6.454 | 5726/0.502 |
| Data/Reflections/Parameters | 35107/6455 | 66326/8875 | 69444/7938 | 18023/4567 | 33777/5726 |
| Goodness of fit on F² | 4.186 | 4.186 | 4.186 | 4.186 | 4.186 |
| Final R Indices | | | | | |
| wR² = 0.0678 | | | | | |
| CCDC | 1858573 | 1858576 | 1858577 | 1858574 | 1858575 |
Table 2. Comparative Cell Parameters Data* from SXRD and PXRD

| crystal form | SXRD | PXRD |
|--------------|------|------|
| SII-QUE I    |      |      |
| SII-QUE II   |      |      |
| SII-3-A-DHBA I |      |      |
| SII-3-A-DHBA II |     |      |
| SII-3-A-DHBA III |    |      |
| SII-3-A-DHBA IV |    |      |
| SII-RIB I    |      |      |
| SII-RIB II   |      |      |
| SII-TAR I    |      |      |
| SII-TAR II   |      |      |
| SII-TAR III  |      |      |
| SII-TAR IV   |      |      |
| SII-CAP I    |      |      |
| SII-MBG      |      |      |
| SII-3-HBA II |      |      |
| SII-3-HBA IV |      |      |

* R-factor for SXRD and \( R_{wp} \) for PXRD.
Table 3 Coformers Chosen in This Study Based on the Difference between the Interaction Site Pairing Energies of Sildenafil and the Pure Components, $\Delta E$

| coformer                       | $\Delta E$/kJ mol$^{-1}$ |
|--------------------------------|--------------------------|
| quercetin                      | 28.1                     |
| resveratrol                    | 24.0                     |
| phloroglucinol                 | 23.8                     |
| 3,4-dihydroxybenzoic acid      | 21.7                     |
| resorcinol                     | 19.3                     |
| tartaric acid                  | 18.2                     |
| caffeic acid                   | 17.8                     |
| reyo-ino sittol                | 15.7                     |
| tert-butylhydroquinone         | 13.8                     |
| methyl galate                  | 13.5                     |
| 3-hydroxybenzoic acid          | 13.1                     |
| 4-hydroxybenzoic acid          | 12.9                     |
**Table 4** Cocrystal Screening Coformers pKa’s and Estimated Probability of Proton Transfer

| coformer               | reported pKₐ | ΔpKₐ | P (%) |
|------------------------|--------------|------|-------|
| quercetin              | 8.45[^85]    | -1.67 | 0     |
| resveratrol            | 8.49[^96]    | -1.71 | 0     |
| phloroglucinol         | 7.97[^97]    | -1.19 | 8     |
| 3,4-dihydroxybenzoic acid | 4.40[^97]  | 2.38  | 68    |
| resorcinol             | 9.44[^97]    | -2.66 | 0     |
| tartaric acid          | 3.03[^97]    | 3.75  | 92    |
| caffeic acid           | 4.47[^96]    | 2.31  | 67    |
| myo-inositol           | 12.29[^96]   | -5.51 | 0     |
| 1-buthylhydroquinone   | 9.94[^96]    | -3.16 | 0     |
| methyl gallate         | 8.11[^85]    | -1.33 | 5     |
| 3-hydroxybenzoic acid  | 4.08[^98]    | 2.7   | 74    |
| 4-hydroxybenzoic acid  | 4.57[^98]    | 2.21  | 66    |
Table 5 Classification of Multicomponent Crystals with a Piperazine and a Carboxylic Group in the CSD

| Class   | No. of Structures | %   |
|---------|-------------------|-----|
| Salt    | 184               | 75  |
| Cocrystal | 38              | 15  |
| Hybrid  | 25                | 10  |