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Mini Review

The Solid State Landscape of the Sildenafil Drug

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ABSTRACT

Sildenafil, the active ingredient of the drug developed by Pfizer for the treatment of erectile dysfunction was firstly synthesized in 1989 in the United Kingdom and since then it has become one of the most prescribed drugs for sexual performance in the western world with more than 2.7 million prescriptions in the US in 2021. Since its discovery, this drug compound has attracted the interest of formulators and crystallographers, with a high number of crystal forms of sildenafil being found and characterized, including polymorphs, hydrates, solvates, salts and cocrystals, converting it in one of the most promiscuous multicomponent crystal former drugs in the pharmaceutical sciences arena. In this minireview, the polymorph, pseudopolymorph and multicomponent solid forms landscape of sildenafil is presented through a comprehensive compilation of their 42 solid forms reported in literature.

Introduction

Sildenafil, broadly known by its commercial name of Viagra (and with the IUPAC name of 5-{2-Ethoxy-5-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one), is a drug used in the form of the citrate salt for the treatment of erectile dysfunction (ED). The discovery of Viagra[1] in the 90s by Pfizer is undoubtfully one of the greatest breakthroughs in the treatment of ED. Within the first two months of being on the US market Viagra was prescribed to more than two million patients.[2] Two years later Viagra was prescribed at a pace of seven pills a second, by the end of the decade (according to Simon Campbell)[3] "more than 150 million tablets had been dispensed worldwide over 100 countries. Since then Viagra has made Pfizer more than $1.4 billion a year.

Viagra is a potent selective inhibitor of PDE5 (phosphodiesterase type 5) which inhibits cGMP (cyclic guanosine monophosphate) break down, prolonging vasodilatory response and improving erection by enhancing relaxation of the corpus cavernosal smooth muscle.[4] However, the idea of smooth muscle relaxation causing erection was controversial at the time since the most extended belief was that penile erection required contraction of drainage vascular channels allowing blood to be trapped, until a British neurophysiologist, Dr. Giles Brindley performed a live demonstration on himself at the annual American Urological Association in Las Vegas in 1983, injecting a muscle relaxation drug (phenoxybenzamine) directly into his corpus cavernosum showing to the world (and to the shocked audience who could not only see the exposed erection but touch it)[5] that erections could be caused by penile vasodilation and opening the door to a new and exciting new therapy to treat ED (erectile dysfunction).[6]

1992 the molecule responsible to cause the smooth muscle relaxation was identified and published in Science which called the Nitric Oxide "The molecule of the year".[7] This small neurotransmitter is endogenously synthetised by the penis nerves cells binding to guanylate cyclase receptors and increasing cyclic guanosine monophosphate (cGMP) levels, producing smooth muscle relaxation leading to vasodilation and consequent increased blood flow to the corpus cavernosum and an erection. In 1998 Dr. Ignarro, Dr. Furchgott and Dr. Murad were awarded the Nobel prize in Physicology or Medicine for their work showing the role of Nitric Oxide.[8]

In the late 80s one of the Pfizer cardiovascular research programs (at Sandwich, UK) was focussed on finding new selective PDE5 inhibitors for the treatment of high blood pressure and angina (chest pain caused by reduced blood flow to the heart), however clinical trials performed with the potent PDE5 inhibitor candidate (Sildenafil citrate) were disappointing.[9,10] On top of lack of significant clinically effect on the hemodynamic readouts subjects complained of side effects, including an unexpected one, an increased frequency (and quality) of erections. Fortunately scientist at Pfizer realised of the huge potential this compound could have just before the clinical program was closed, and in 1993 clinical trials started in Bristol (UK) on sixteen men with ED.[11] One of

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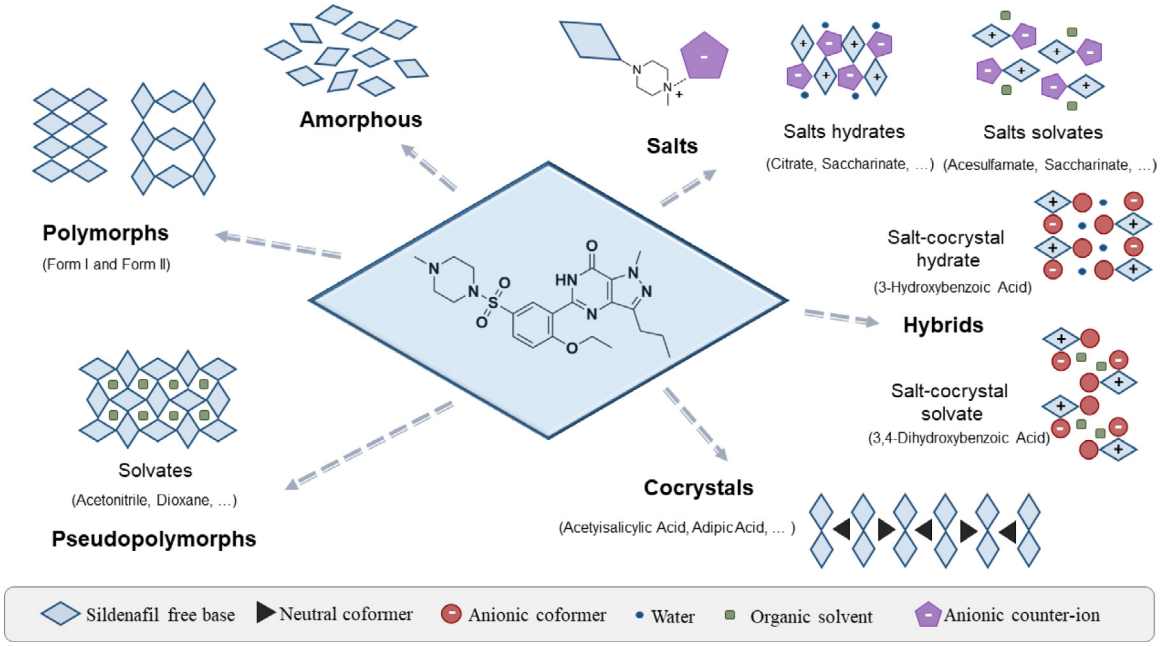

Fig. 1. The Sildenafil solid forms landscape according to the crystal structures reported.

us (A.LL.) met Nick Terrett while working at the Pfizer Institute for Pharmaceutical Materials Science at the University of Cambridge in UK in 2006 (funnily enough to discuss the patent of a method invented by A.LL. during that period to generate the most stable polymorph of pharmaceutical drugs).[12] Nick was then the Head of Chemistry at the Cambridge MA Pfizer site, and he was several years before the Lead chemist (and inventor) of the Sildenafil program. During dinner that night Nick pointed out the extreme complexity of setting up objective parameters to define success for the Sildenafil clinical program, since sexual stimulation would be still a necessary component of the program and objective evaluation of the level of satisfaction with the quality of erections is rather subjective. The solution was initially using a device called the RigiScan to monitor erections (a device the size of an electric razor resembling a large computer mouse coupled with a calculator),[13,14] and later in Phase III clinical trials, a combination of patient (and partner's) diaries and responses to questionnaires.[15] The clinical team at Pfizer started to suspect they had something big in their hands when participants in the clinical trials (and their partners also) were calling requesting more tablets (claiming they had lost them or flushed the extra tablets accidentally down the toilet) and many did not want to return excess samples of Sildenafil once trials were over, so profound had been the benefits to those patients. Pfizer received a lot of letters from the volunteers requesting to have access to the drug once the trials finished. Pfizer decided to allow volunteers to receive the drug for free on an open-label extension.

On a Friday morning at 10:57 of a 27th of March in 1998 Pfizer's office in D.C. received the fax from the U.S Food and Drug Administration giving Pfizer the approval of the new miracle drug. Since then a high number of crystal forms of Sildenafil have been found and characterized, including polymorphs, hydrates, solvates, salts and cocrystals, converting it in one of the most promiscuous multicomponent crystal former drugs. In this review, the polymorph, pseudopolymorph and multicomponent solid forms landscape of Sildenafil is presented in-depth through a comprehensive compilation of their 42 solid forms reported in literature.

The Sildenafil solid forms

It is well recognized that polymorphism is a very common phenomenon, with 90% of organic compounds existing in multiple crystalline forms.[16] This variety of solid modifications can have a strong impact during the development of a pharmaceutical drug formulation since the potential interconversion between polymorphs can have important consequences in terms of solubility, stability and last but not least intellectual property implications.[17–19] Thus, along the lifetime of a drug the investigation of the polymorph landscape continues in order to ensure the control of the best suited solid form of the commercial formulation and to reduce the risk of unexpected phenomena such as disappearing[20,21] and late appearing polymorphs.[22,23] Sildenafil has been the subject of study of numerous research works in the field of solid state chemistry which have pictured a very rich landscape of solid forms diversity. Fig. 1 shows a schematic description of the known solid forms of Sildenafil, which include all five categories in which a pharmaceutical compound can exist: amorphous phases, anhydrous polymorphs, solvates, salts and cocrystals. Thus, with the aim to classify them, the most relevant structural or physicochemical issues are presented in this review and summarized in Table 1.

Anhydrous forms of the Sildenafil free base

The free base exists as two anhydrous polymorphs (Forms I[24] and II[25]) and an amorphous form.[37] Form I is the most stable one and it is usually found when the free base is crystallized in most organic solvents except in acetonitrile. In this solvent a solvate is obtained, which transforms into anhydrous Form II prior isomorphous desolvation. The crystal structure of both forms show a strong intramolecular hydrogen bond between the ethoxy and the pyrimidine groups with subtle conformational differences, which are considered molecular adjustments of the same gas phase conformation. Moreover, the two polymorphs are monotropically related and a non-crystallographic inversion center transforms one polymorph into the other (Fig. 2).

Table 1
Reported solid forms of Sildenafil.

CCDC refcode	Cocrystal or salt former	Solid form	Year
QEGTUT[24]	None	anhydrous	2012
QEGTUT01[25]	None	anhydrous	2018
QEGTUT02[25]	None	anhydrous	2018
HEZGEB[25]	Propanenitrile	solvate	2018
HEZMAD[25]	Acetonitrile	solvate	2018
RIBVAC[26]	Hemianisole	solvate	2018
RIBVIK[26]	Chloroform	solvate	2018
RIBVOQ[26]	1,4-dioxane	solvate	2018
RIBXOS[26]	hemitoluene	solvate	2018
CIHFIL[27]	acesulfamate	salt	2018
WOYHAV[28]	salicylate	salt	2015
YAJHEZ[29]	thiosaccharinate	salt	2017
YIWWIM[30]	hemikis(oxalate)	salt	2013
YIWXAF[30]	hemikis(glutarate)	salt	2013
QEKWEJ[31]	saccharinate	salt	2006
FEDTEO[32]	citrate monohydrate	salt hydrate	2005
KAJYIG[33]	citrate hemihydrate	salt hydrate	2016
YIWWOS[30]	hydrogenfumarate trihydrate	salt hydrate	2013
YIWWUY[30]	hemikis(succinate) monohydrate	salt hydrate	2013
QEMLOK[31]	saccharinate dihydrate	salt hydrate	2006
QISYAV[34]	3-hydroxybenzoate hemitetrahydrofuran sesquihydrate	salt solvate hydrate	2018
CIHFAD[27]	acesulfamate acetonitrile	salt solvate	2018
QEKVEI[31]	saccharinate hemikis(ethanol)	salt solvate	2006
QEKVIM[31]	saccharinate methanol	salt solvate	2006
QEKVOS[31]	saccharinate hemikis(dimethylsulfoxide)	salt solvate	2006
QEKVUY[31]	saccharinate nitromethane	salt solvate	2006
QEKWAF[31]	saccharinate hemikis(pyrrolidinone)	salt solvate	2006
QEKWIN[31]	saccharinate formamide	salt solvate	2006
QEKWOT[31]	saccharinate hemikis(1,4-dioxane)	salt solvate	2006
QEKWUZ[31]	saccharinate hemikis(ethylene glycol)	salt solvate	2006
QEMLEA[31]	saccharinate hemikis(dimethylformamide)	salt solvate	2006
QEMLIE[31]	saccharinate acetonitrile	salt solvate	2006
QISXUO[34]	tartrate hemiisopropanol	salt solvate	2018
QISYEZ[34]	3-hydroxybenzoate 3-hydroxibenzoic acid monohydrate	hybrid salt-cocrystal hydrate	2018
QISYOJ[34]	3,4-dihydroxybenzoate 3,4-dihydroxibenzoic acid monohydrate	hybrid salt-cocrystal hydrate	2018
QISYID[34]	3,4-dihydroxybenzoate 3,4-dihydroxibenzoic acid diacetonitrile	hybrid salt-cocrystal solvate	2018
DISXOU[35]	acetylsalicylic acid	cocrystal	2014
YIWXEJ[30]	adipic acid	cocrystal	2013
YIWXIN[30]	pimelic acid	cocrystal	2013
YIWXOT[30]	suberic acid	cocrystal	2013
YIWXUZ[30]	sebecic acid	cocrystal	2013
UMUXUY[36]	diresorcinol	cocrystal	2020

The amorphous form can be prepared by rapid cooling from the melt of the crystalline free base. The supercooled solid shows a remarkable kinetic resistance towards recrystallization for long periods of storage at temperature values which are 30 °C lower than its glass transition (T_g = 57 °C, determined by DSC at a heating rate of 10 °C/min). However it shows a high tendency to recrystallize above this temperature.[37]

Solvates of Sildenafil free base

There are no hydrates reported for the free base. However, acetonitrile and propanenitrile solvates have been characterized. Two isostructural acetonitrile solvates exist in two different Sildenafil/acetonitrile molar ratios (2:1 and 1:1), being the 2:1 solvate the precursor of the anhydrous Form II, which is considered to be a desolvate since Form II has only been produced from desolvation and not from crystallization. Moreover, the propanenitrile solvate (1:1 molar ratio) shows a crystal structure with similar packing than that of anhydrous Form I and its desolvation produces this anhydrous form.[25]

It is important to highlight that a strong intramolecular hydrogen bond formed in a six-members ring supramolecular synthon between the ethoxy oxygen and the pyrimidine hydrogen is present in most of the crystal structures of the multicomponent forms of Sildenafil (34 crystal structures). However, this interaction is broken in the solvates with toluene, anisole and dioxane, due to the formation of $\pi-\pi$ stacking interactions between the pyrimidine ring and the aromatic surface of the solvent molecules in cage-like assemblies.[26] Interestingly, in the crystal structure of the human phosphodiesterase 5 protein (cGMP-specific PDE5, the target of Sildenafil for the treatment of erectile dysfunction) complexed with Sildenafil[38] the intramolecular hydrogen bond is also broken since a glutamine residue of the protein binds strongly the amide group of the pyrimidine ring of Sildenafil, suggesting a potential strategy of intermolecular interactions for cocrystal design (Fig. 3).

Multicomponent solid forms of Sildenafil

This is by far the most numerous group of crystal forms of Sildenafil. The need for improving the water solubility and the speed of action of the drug (solubility of the free base is 5–10 mg/L)[31] has driven the production of a big number of salts by taking advantage of the presence of a tertiary amine in its chemical structure. The first salt to be marketed was the citrate with the commercial name of Viagra. Initially, the crystal structure of the citrate salt (ref code FEDTEO) was reported as a monohydrate,[32] but a later study of the crystal structure by Abraham et al.[33] shown that when the occupancy factor of the water molecules was refined then the structure fitted better to

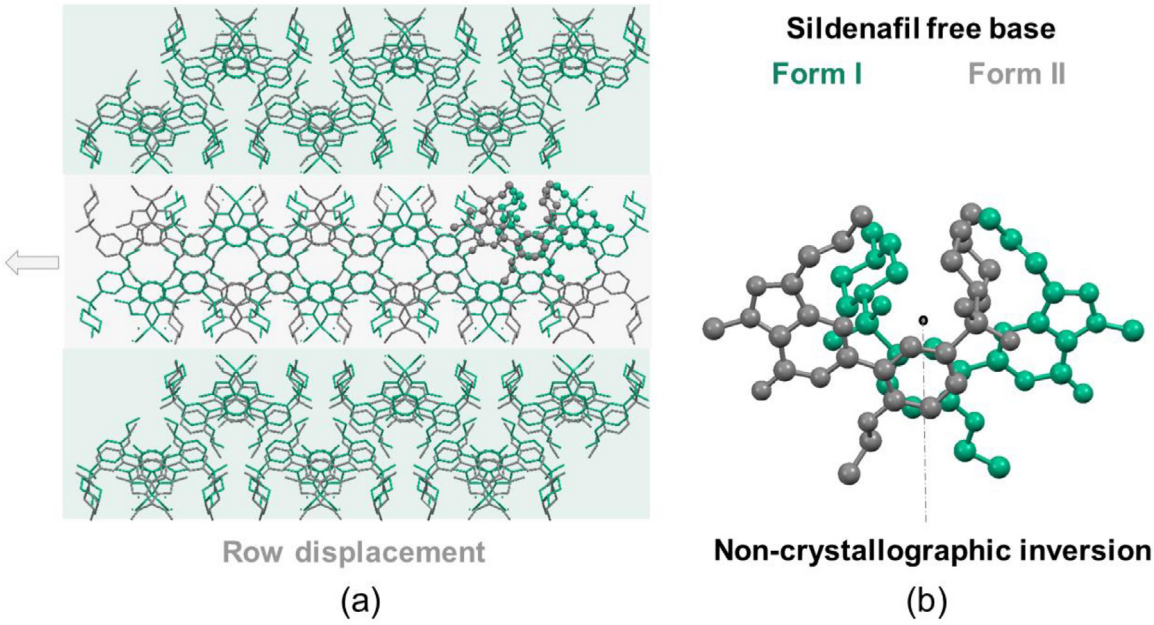

Fig. 2. (a) Overlay of crystal structures of Forms I and II showing a layer with the non-crystallographic inversion and (b) Representation of the non-crystallography inversion.

a hemihydrate, with water molecules filling channels. Moreover, DVS and TGA analyses[33] together with a solid-state NMR study also confirmed the partial occupancy of the water site and the non-stoichiometric nature[39] of the citrate salt hydrate.[40] (Fig. 4) On the other hand, anhydrous Sildenafil citrate is reported to be formed through dehydration at 40°C or at 0% RH, but the crystal structure has not been solved.[33]

Curiously, neither Pfizer's patent[41] nor commercial information of Sildenafil citrate[42] specifies the degree of hydration of the marketed product.

On the other hand, in spite of good general performance of the citrate salt but due to some limitations in terms of solubility, bioavailability and a bitter taste other carboxylic acids have been tried to prepare alternative salts.[30] In this sense, Desiraju et al. have prepared and characterized a set of salts and cocrystals of Sildenafil with dicarboxylic acids (oxalic, fumaric, succinic, glutaric, adipic, pimelic, suberic and sebacic) and studied their solubility and pharmacokinetics profiles, being the glutarate salt the one with the highest water solubility and bioavailability, increasing by more than twice those for the citrate salt.

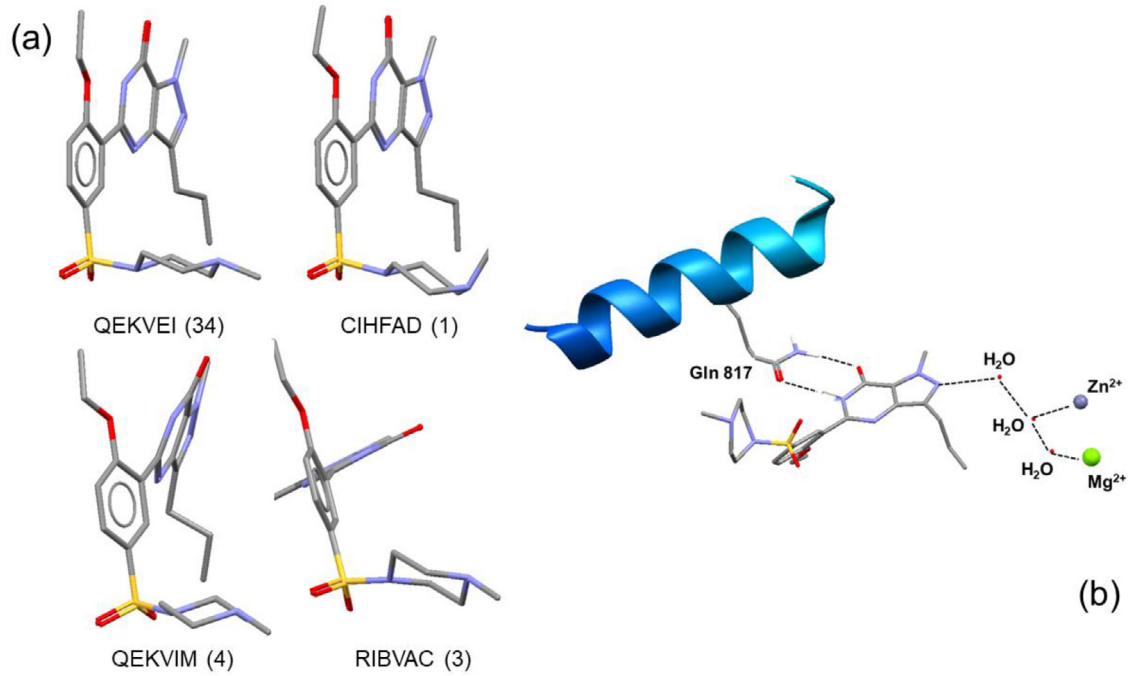

Fig. 3. (a) The four conformations observed in all the reported Sildenafil crystal structures. (b) Binding pocket of the complex formed by the cGMP protein and Sildenafil, showing the interaction with the GLN 817 residue (according to Sung et al. determination).[38] Hydrogens have been partially omitted for clarity.

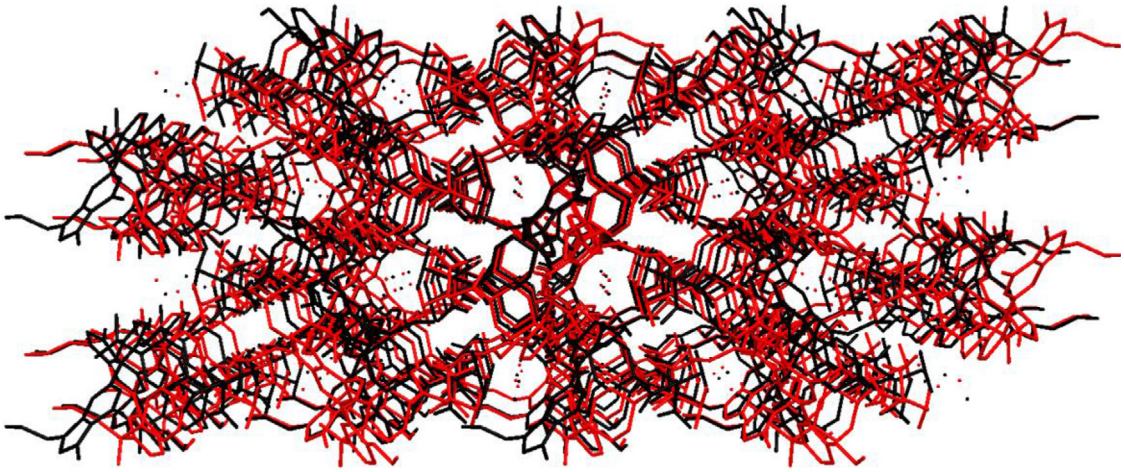

Fig. 4. Overlay of both crystal structures of Sildenafil citrate reported: monohydrate (FEDTEO, black) and hemihydrate (KAJYIG, red) showing the water channels of this non-stoichiometric hydrate.

From a regulatory point of view the formation of a salt or a cocrystal can have important implications since it is necessary for applicants presenting a new drug application to the FDA to demonstrate that the API and the coformer are present in the crystal lattice interacting non ionically, which makes crucial the location of the most acidic proton of the counterparts.[43] The moderate basicity of the piperazine moiety of Sildenafil (pKa = 6.78)[44] makes possible both salt and cocrystal formation with an acidic compound, being the determination of the proton location (deduced by crystallographic means) the only way to assess the formation of a neutral or ionic solid form.

Moreover, a partial proton transfer from an acidic coformer can produce the so-called hybrid salt-cocrystals,[34] which are crystal forms containing at the same time the active ingredient or the coformer in both ionic and neutral form in the lattice. This is due to the existence of a "salt-cocrystal continuum",[45,46] which is a region that usually exists when the difference between the pKa of the API and the coformer falls between 0 and 3.

On the other hand, an important limitation of Sildenafil is that it is contraindicated in men with cardiovascular issues since it makes arteries wide, causing a decrease of blood pressure. Thus, alternative multicomponent solid forms including acetilsalycilic acid as the coformer, which confers protective cardiac effects have been studied.[35]

Sildenafil, although a very hydrophobic drug shows a great variety of functional groups with the ability to form hydrogen bonds, as the theoretical molecular electrostatic potential surface shows (Fig. 5). A computational cocrystal screen through the

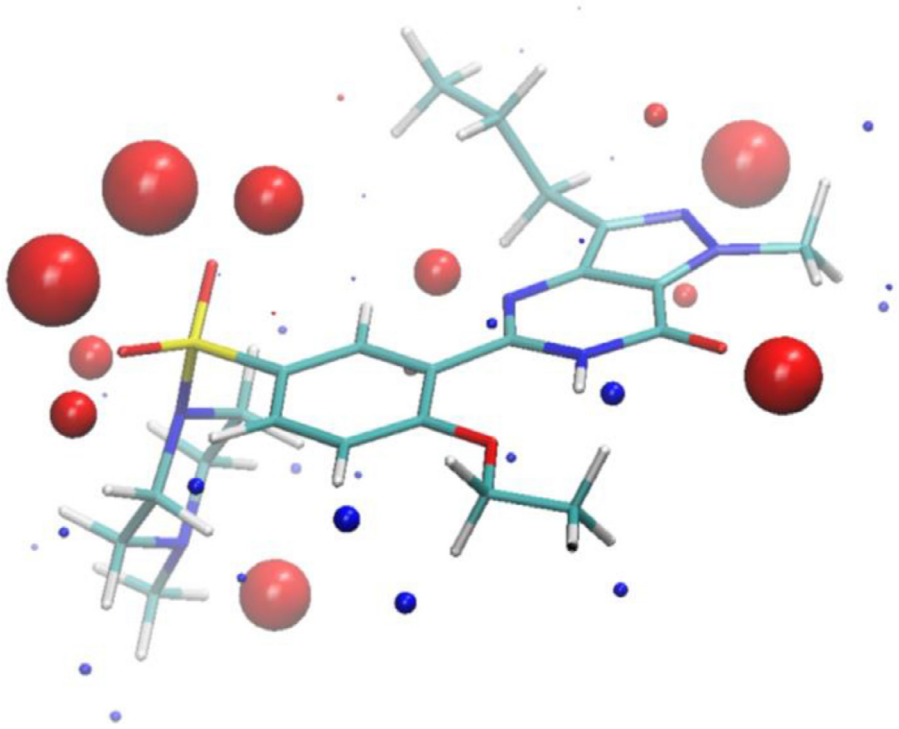

Fig. 5. Surface Site Interaction Points calculated for the Sildenafil free base. H-bond donors are represented as blue spheres and H-bond acceptors as red spheres. The volume of the sphere is proportional to the strength of the potential intermolecular interaction.

calculation of potential hydrogen bonding sites on the surface of Sildenafil guided the design of an experimental search with the discovery of 23 new solid forms, including salts, cocrystals and hybrid salt-cocrystals. In the case of acidic coformers (tartaric acid, 3-hydroxybenzoic acid, and 3,4-dihydroxybenzoic acid) salts and hybrid salt-cocrystals were obtained (as determined through the crystal structures analysis) with the tartrate salt showing promising water solubility profiles.[34]

In summary, the need for the improvement of the poor water dissolution performance of most hydrophobic drugs have motivated in the last decade the development of hundreds of research projects both in academy and industry which have generated a huge corpus of new data about solid forms of APIs. This has allowed scientific disciplines such as Supramolecular Chemistry and Crystal Engineering to be provided with a deeper knowledge of the matter that has been successfully used to develop new experimental and computational approaches, which can assist the discovery of new crystal forms with potential benefits mainly in terms of solubility and stability.[47,48] The case of Sildenafil can be considered paradigmatic in the sense that it is one of the pharmaceutical compounds with the highest number of known solid forms covering all the possible chemical and crystallographic situations in which a drug compound can exist, including amorphous and crystalline anhydrous, hydrate, solvate, desolvate, salt, cocrystal and ionic cocrystal forms.

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