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Preparation and crystal structure of sildenafil salicylate

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A new two-component drug solid comprising the active pharmaceutical ingredients sildenafil and salicylic acid (1:1) was prepared in the form of an addition salt and characterized by single crystal X-ray diffraction analysis.

Solid drug molecules can occur as polymorphs, cocrystals, salts, hydrates/solvates or amorphous substances without changing their intrinsic chemical structures. Thus, an important step in the development of drugs is the selection of an appropriate solid form of an active pharmaceutical ingredient (API). The tuning of the physicochemical properties of a single API is limited by a finite number of inactive pharmaceutically acceptable acids, bases, polymorphs, and hydrates/solvates.[1–3]

Human health disorders, including cardiovascular, metabolic and autoimmune diseases, are treated by a combination of two or more drugs.[4] Up to 25% drugs on the market are fixed drug combinations (FDCs) containing different APIs.[5] As an alternative to FDCs, it is possible to assemble different APIs in one crystal lattice by cocrystallization. These new multicomponent drug solids may be salts, cocrystals or their mixtures.[6–11] According to drug combination rational principles, such a combination is feasible when drugs have (i) synergy effects, (ii) comparable therapeutic doses, (iii) comparable half-lives, (iv) different metabolism pathways, (v) different mechanisms of action and different targets/receptors.[12]

Here, we describe the preparation and crystal structure of a pharmaceutical solid comprising sildenafil (**sil**) and salicylic acid (**sa**). Sildenafil is used in treatment for erectile dysfunction because it selectively inhibits cGMP-specific phosphodiesterase type 5.[13,14] Salicylic acid is well known for its ability to reduce pain and fever.[15] Sildenafil in citrate form, marketed as Viagra®, is the first effective oral drug for the treatment of sexual dysfunctions approved by US Food and Drug Administration in 1998.[16,17] The crystal structure of **sil** citrate monohydrate has been investigated by Yathirajan *et al.*[18] Recently,[19] we reported the crystal structure of the **sil** base. Sildenafil forms salts with saccharine[20] and oxalic, fumaric, succinic and glutaric acids and cocrystals with adipic, pimelic, suberic and sebacic acids.[1] The cocrystal of **sil** with acetylsalicylic acid (**asa**, aspirin) has been described.[17] The formation of (**sil**)$^+$(**asa**)$^-$(**sa**) cocrystal salt was also confirmed by powder diffraction analysis and other physicochemical methods.[17] Since **sil** is contraindicated for men suffering from cardiovascular diseases, the rationality of the (**sil**)(**asa**) combination is based on the fact that **asa**, having an anti-platelet activity, is commonly prescribed as a long-term preventative agent for combating heart attack and stroke.[21]

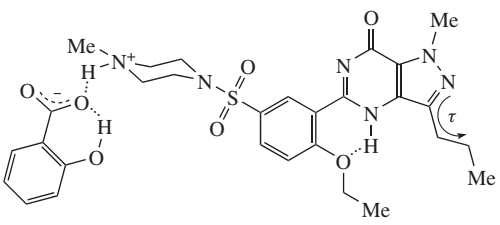

Figure 1 Chemical structure of (**sil**)$^+$(**sa**)$^-$.

So far as **sa** is an active metabolite of **asa**, arguments[17] for the rationality of (**sil**)(**asa**) and (**sil**)$^+$(**asa**)$^-$(**sa**) compositions can be transferred to the (**sil**)$^+$(**sa**)$^-$ (Figure 1).

A solid form of (**sil**)$^+$(**sa**)$^-$ was obtained *via* slow solution crystallisation. Sildenafil and salicylic acid were taken in a stoichiometric ratio of 1:1 [30 mg (0.063 mmol) of **sil** and 9.28 mg (0.063 mmol) of **sa**] and dissolved in 3 ml of methanol. Slow solvent evaporation gave good quality colourless crystals after three days. The **sil** base was obtained from **sil** citrate monohydrate using a published procedure.[19] Our attempt to cocrystallize **sil** with benzoic acid was unsuccessful.

Compound (**sil**)$^+$(**sa**)$^-$ crystallises in the triclinic system, space group $P\bar{1}$ (Z = 2), with the sildenafil cation and the salicylate anion in an asymmetric unit (Figure 2).†

The methylated N atom of a piperazine fragment is most basic (pK_a = 8.7)[1] and most suitable for hydrogen bond formation. Proton transfer from **sa** (pK_a = 2.8)[15] to the N-methylated piperazine

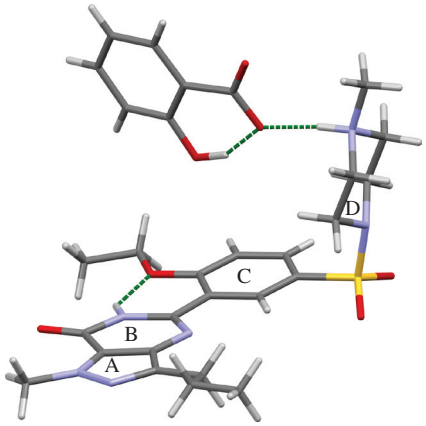

Figure 2 X-ray crystal structure of (**sil**)$^+$(**sa**)$^-$ showing hydrogen bonds as dashed line.

† *Crystal data for* (**sil**)$^+$(**sa**)$^-$: $(C_{22}H_{31}N_6O_4S)^+(C_7H_5O_3)^-$ (M = 612.71), triclinic, $P\bar{1}$, a = 9.5030(3), b = 11.6242(4) and c = 14.2074(6) Å, α = 99.167(1)°, β = 108.370(1)°, γ = 92.229(2)°, V = 1463.75(9) Å^3, T = 173(2) K, Z = 2, Z' = 1, μ(MoKα) = 0.168 mm^{-1}, 13 192 reflections measured, 8539 independent reflections (R_{int} = 0.059), $R_{1(obs)}$ = 0.0678, $wR_{1(obs)}$ = 0.1537, $R_{1(all)}$ = 0.1712, $wR_{1(all)}$ = 0.1230, S = 0.969. The compound melts between 179–182 °C.

CCDC 990216 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

Table 1 Selected dihedral and torsion angles of a sildenafil moiety in crystal structures.

Structure	(A+B)–C/°	C–D/°	τ/°
(**sil**)$^+$(**sa**)$^-$ (1:1)	2.7	81.1	–15.1(3)
(**sil**)(**asa**) cocrystal (1:1)[17]	4.4	76.9	–5(1)
sil base[19]	5.6	89.8	–135.4(4)
(**sil**)$^+$ citrate (H_2O) (1:1:1)[18]	11.6	81.3	78.6(8)
(**sil**)$^+$ saccharinate (1:1)[20]	2.4	78.4	–20.1(5)
(**sil**)$^+$ saccharinate ($2H_2O$ clathrate) (1:1:2)[20]	3.0	85.8	–6.9(4)
(**sil**)$^+$ saccharinate (ethanol clathrate) (1:1:0.5)[20]	3.0	85.9	8.7(3)
(**sil**)$^+$ saccharinate (methanol clathrate) (1:1:1)[20]	36.7	75.6	–77.7(6)
(**sil**)$^+$ saccharinate (DMSO clathrate) (1:1:0.5)[20]	2.7	86.3	8.6(9)
(**sil**)$^+$ saccharinate (nitromethane clathrate) (1:1:1)[20]	2.8	87.6	–10.3(4)
(**sil**)$^+$ saccharinate (pyrrolidone clathrate) (1:1:0.5)[20]	2.6	85.4	–10.3(6)
(**sil**)$^+$ saccharinate (formamide clathrate) (1:1:1)[20]	3.1	85.6	–8.5(3)
(**sil**)$^+$ saccharinate (1,4-dioxane clathrate) (1:1:0.5)[20]	2.3	86.8	–11.1(3)
(**sil**)$^+$ saccharinate (ethylene glycol clathrate) (1:1:0.5)[20]	3.1	84.5	–6.1(3)
(**sil**)$^+$ saccharinate (DMF clathrate) (1:1:1)[20]	2.4	86.3	8.6(2)
(**sil**)$^+$ saccharinate (acetonitrile clathrate) (1:1:1)[20]	2.9	86.3	9.6(2)
(**sil**)$^+$ oxalate (1:0.5)[1]	6.6	67.9	96.9(2)
(**sil**)$^+$ fumarate (H_2O) (1:1:3)[1]	27.4	89.9	–124.1(2)
(**sil**)$^+$ succinate (1:1)[1]	3.4	74.3	–3.0(6)
(**sil**)$^+$ glutarate (1:0.5)[1]	7.0	71.0	–92.8(9)
(**sil**)$^+$ adipic acid cocrystal (1:1)[1]	8.8	71.4	–75.2(3)
(**sil**)$^+$ pimelic acid cocrystal (1:0.5)[1]	9.5	72.2	–81.4(2)
(**sil**)$^+$ suberic acid cocrystal (1:0.5)[1]	4.8	75.2	–0.6(3)
(**sil**)$^+$ sebacic acid cocrystal (1:0.5)[1]	7.6	74.4	–77.7(5)

of **sil** [producing N–H···O type intermolecular hydrogen bond, $d_{D\cdots A}$ = 2.626(3) Å] confirmed salt formation. The N–H···O and O–H···O intramolecular bonds were also found in **sil** and **sa** moieties, respectively (see Online Supplementary Materials for hydrogen bond geometry).

For comparing the conformations of sildenafil moieties in different crystal structures, we denoted the pyrazole, pyrimidine, phenyl and piperazine rings in the sildenafil molecule by A, B, C and D, respectively, and introduced a torsion angle τ [N(2)–C(1)–C(18)–C(19), Figure 1] to characterize the orientation of a propyl group.

Geometrical parameters given in Table 1 show that the sildenafil molecule is built from a rigid central core fragment consisting of a π-conjugated system of pyrazolopyrimidone and a phenyl ring. In 21 out of the total 24 crystal structures listed in Table 1, a dihedral angle (A+B)–C assumes the values less than 10°. The largest deviation from planarity was observed in (**sil**)$^+$ saccharinate (methanol clathrate) (1:1:1) with an (A+B)–C angle of 36.7°. The dihedral angle C–D lies in a narrow range from 71.0° to 89.9°. This means that the bulky methylpiperazine-sulfonyl fragment has limited rotation freedom with respect to the central core fragment. In all the test structures, the ethoxy group lies in the plane of the phenyl ring. The only flexible part of the molecule is the propyl group, which can adopt three different positions. For 10 crystal structures, the propyl group lies close to the (A+B+C) plane with τ angles within ±10°. In 12 cases, the propyl group is turned out of the (A+B+C) plane and situated on the same side as the methylpiperazine fragment and in 2 cases, on the side opposite to the methylpiperazine fragment.

In conclusion, a new multicomponent drug solid comprising sildenafil and salicylic acid was designed according to drug combination rational principles and prepared in crystalline form. Its crystal structure has been determinated by a single-crystal X-ray structure analysis. Geometrical analysis of twenty four crystal forms of sildenafil revealed conservatism of sildenafil molecule to conformation changes except for propyl group. The 'rigidity' of the molecule is aimed by intramolecular hydrogen bond found in all crystal structures. The insufficient quality of multicomponent crystals and hence the limited accuracy of X-ray experiments prevents the assignment of the structure to a salt or cocrystal. In contrast to published results,[17] where a decision on whether the (**sil**)(**asa**) solid is a salt or a cocrystal was based on ATR-IR and ^{15}N CP-MAS NMR spectroscopic data, we detected proton transfer by difference electron density calculations and the refinement of hydrogen positions.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.01.018.

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