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COMMUNICATION

Crystal engineering of multiple-component organic solids: Pharmaceutical cocrystals of tadalafil with persistent hydrogen bonding motifs†

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Pharmaceutical cocrystals of tadalafil with methylparaben, propylparaben and hydrocinnamic acid have been prepared and characterized. The crystal packing observed in the three resulting cocrystals reveals that tadalafil molecules form persistent hydrogen-bonded chains which accept additional hydrogen bonds from the OH moieties of the respective coformers.

It is well recognised that the supramolecular interactions in crystalline organic solids can profoundly impact the physicochemical properties of a particular crystal form.[1,2] Crystal engineering has been employed as a useful tool for the synthesis of crystal structures with desired supramolecular arrangements.[3,4] However, the ultimate goal of crystal engineering is to synthesize pre-designed crystal structures with desirable properties that are based solely on the knowledge of the molecular components.[3] In this context, the "supramolecular synthon approach", in which structure and composition of multiple component crystals are controlled using previously identified robust intermolecular interactions, has proven to be a particularly reliable strategy.[5–7] In the context of pharmaceutical science, crystal engineering has been successfully employed for the discovery of pharmaceutical salts[8] and cocrystals[9–12] of active pharmaceutical ingredients (APIs), thereby creating opportunities to fine tune the physicochemical and pharmacokinetic properties of the APIs. Carbamazepine, for example, forms cocrystals with a variety of carboxylic acids and amides because of the self-complementary nature of amide-carboxylic acid and amide-amide functional groups.[13] As a result, a series of carbamazepine cocrystals were synthesized and characterized.[14] Among those novel crystal forms, the cocrystal of carbamazepine and saccharin exhibited significantly improved physical stability and favourable pharmacokinetics in dogs compared to the original API.[15] The cocrystal of carbamazepine and nicotinamide also exhibited superior physical properties.[16] It has now become evident that crystal engineering facilitates the discovery of pharmaceutical cocrystals and that resulting property enhancements can be significant enough to be clinically relevant. In this contribution, we report the application of crystal engineering to the synthesis of tadalafil cocrystals and address the crystal packing in the resulting cocrystals.

Tadalafil (TDF, Fig. 1) is currently used for the treatment of erectile dysfunction (ED) under the brand name Cialis®. TDF is a cGMP (cyclic gaunosine monophosphate) specific phosphodiesterase 5 (PDE5) inhibitor.[17,18] This medication stops the breakdown of cGMP in endothelial cells in the corpus cavernosum of the penis by inhibiting PDE5. This effect results in vasodilation and a subsequent increase of blood flow into the corporus cavernosum leading to penile erection upon sexual stimulation.[19] TDF is also currently being investigated as a treatment for pulmonary arterial hypertension.[20,21] For ED treatment, TDF is manufactured as a tablet for daily use (2.5 and 5 mg) with doses ranging from 5 up to 20 mg as needed. Among the PDE5 inhibitors that have been approved and marketed, TDF exhibits a longer half life[22] but possibly a slower onset of action.[23] The slower onset could be caused by its low aqueous solubility. TDF,

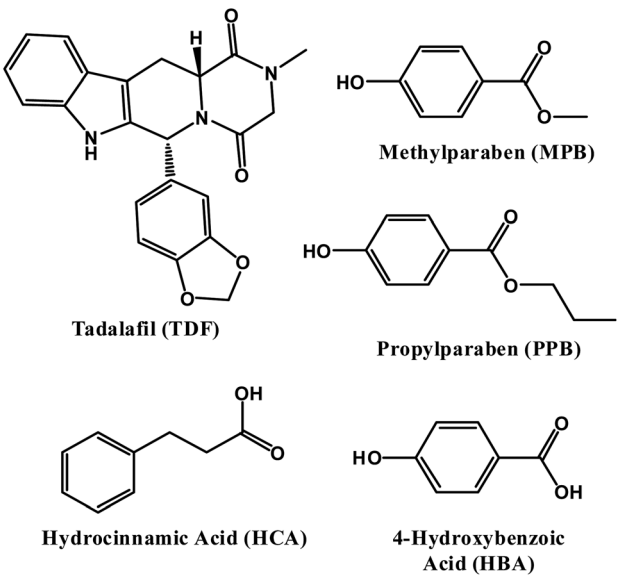

Fig. 1 Molecular structures of TDF and its coformers.

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a white powder at ambient conditions, is practically insoluble in water (2 μg mL^{-1}),[24] and is considered a class II drug[22] by the Biopharmaceutics Classification System.[25] In consequence, TDF takes approximately 0.5 to 6 h (T_{max}) to achieve mean peak plasma concentration (C_{max}) in the body, regardless of food intake.[22] Various formulation techniques have been used to improve the solubility and onset of TDF with limited success reported.[26,27] It is believed that modification of the TDF crystal form could offer a promising alternative to enhance the solubility of this API and improve the oral drug absorption, thus enabling faster clinical performance of the drug.

A recent literature search showed that at least eight crystal forms of TDF, including polymorphs and solvates, have been reported,[28] while only one crystal structure of TDF has been deposited (refcode: IQUMAI)[18] in the Cambridge Structural Database[29] (CSD) to date. Due to the existence of lactam and indole moieties in the molecular structure of TDF, it is predisposed to form hydrogen bonds with a second molecule (coformer) in the crystal lattice and it was therefore considered appropriate for cocrystal screening.

To better understand the potential intermolecular interactions of TDF cocrystals, the crystal structure of TDF was analysed. The crystal packing in TDF reveals that adjacent TDF molecules are hydrogen-bonded *via* N–H···O=C interactions [N3-H9···O2: N···O 2.985 Å, H···O 2.09 Å, N–H···O 167.06°] between the indole group of one molecule and the lactam carbonyl group of a neighbouring molecule. The result shows that TDF molecules form supramolecular chains in the crystal lattice along a 2_1 screw axis parallel to the *b*-axis (Fig. 2).[18] In addition, the lactam carbonyl group that is not involved in the supramolecular chain formation interacts with the indole ring of another TDF molecule in an adjacent chain *via* weaker C–H_{arom}···O=C hydrogen bonding. A CSD survey of lactam and indole molecules was also performed. Certain restrictions were placed upon the CSD survey to include relevant crystal structures with atomic coordinates determined, *R*-factor ≤ 0.075, only organic molecules and no ions involved. The result indicated that TDF would be amenable to form cocrystals with coformers that contain alcohol or carboxylic acid moieties, due to the greater propensity for supramolecular heterosynthon *versus* supramolecular homosynthon formation (*i.e.*, formation of carboxylic acid-carboxylic acid or alcohol-alcohol interaction). Specifically, the alcohol and carboxylic acid moieties were approximately five and two times more likely, respectively, to form a supramolecular heterosynthon with the lactam moiety, when compared to the occurrence of the corresponding supramolecular homosynthons, which were found to occur less than 15% of the time. A similar trend was found upon examination of the indole moiety where the tendency for supramolecular heterosynthon formation was *ca.* 50% greater than supramolecular homosynthon formation in the presence of an alcohol or a carboxylic acid.

Methylparaben (MPB, Fig. 1), a pharmaceutically acceptable alcohol, was selected as a potential coformer for cocrystallization with TDF. Thin plate-like single cocrystals of TDF and MPB (**1**) were obtained from an acetonitrile solution with equaimolar amounts of TDF and MPB. The crystal structure of **1** was determined by single crystal X-ray diffraction.‡ **1** crystallizes in the space group $P2_1$ and there is one TDF and one MP molecule in the asymmetric unit. The structure of **1** reveals that adjacent TDF molecules are hydrogen-bonded *via* N–H···O=C interactions [N3-H3A···O6: N···O 2.981(2) Å, H···O 2.12 Å, N–H···O 164.4°] that are similar to those seen in pure TDF. As a result, hydrogen bonded chains of TDF extend along the *b*-axis. The MPB molecules are linked to the supramolecular chains as pendant components *via* O–H···O=C interactions [O7-H1O···O1: O···O 2.746(3) Å, O···H 1.83 Å, O–H···O 166.3°]. The resulting TDF supramolecular chains with additional MPB molecules are interdigitated and thereby form supramolecular sheets as shown in Fig. 3. The interdigitation is supported by C–H_{ester}···π interactions between the methyl group on one MPB molecule and an aromatic ring of another MPB molecule associated with the neighbouring chain. Preparation of **1** was also achieved by solvent-drop grinding[30] and slurry methods. This cocrystal form was also characterized by powder X-ray diffraction (PXRD), Fourier transform infrared spectroscopy (FT-IR), and differential scanning calorimetry (DSC) analyses.

The presence of TDF hydrogen bonded chains in both pure TDF and **1** prompted us to study how persistent this arrangement might be. Therefore, propylparaben (PPB), another pharmaceutically acceptable alcohol, was crystallized in the presence of TDF. Colourless block single crystals of TDF and PPB (**2**) were collected *via* slow evaporation of an acetonitrile solution containing equimolar quantities of TDF and PPB. **2** was also characterized by single crystal

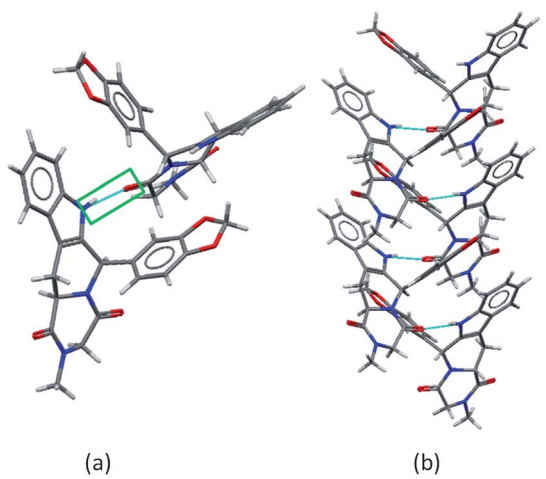

Fig. 2 (a) Hydrogen bonding in crystal structure of TDF (IQUMAI). (b) Supramolecular chains of TDF extended along the *b*-axis.

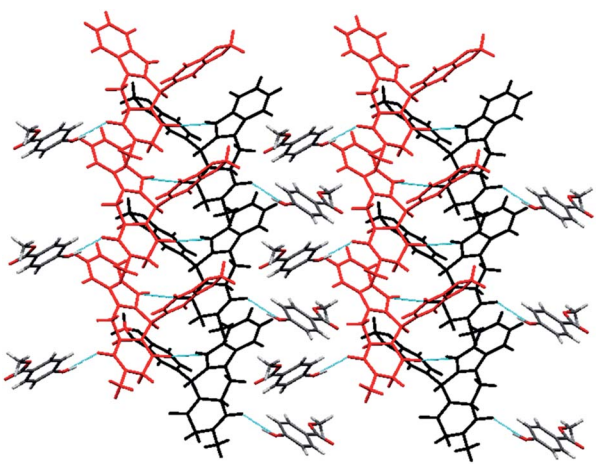

Fig. 3 Crystal packing of **1**.

X-ray diffraction. **2** adopts a similar supramolecular structure to that of **1** and even exhibits similar unit cell parameters. **2** also crystallizes in $P2_1$ with one molecule of TDF and one molecule of PPB in the asymmetric unit. The structure of **2** also exhibits TDF supramolecular chains *via* N–H···O=C hydrogen bonds [N1-H1A···O5: N···O 2.965(3) Å, H···O 2.10 Å, N–H···O 168.3°] between neighbouring TDF molecules. Additionally, PPB molecules are found to be hydrogen-bonded to the TDF chains through O–H···O=C interactions [O1-H1···O4: O···O 2.748(3) Å, O···H 1.91 Å, O···H–O 175.4°]. The resulting assembly adopts the same type of interdigitated close packing seen for **1** (Fig. 4). However, in contrast to **1**, the interdigitation is supported by $C–H_{arom}···O=C$ interactions between adjacent PPB molecules. Synthesis of **2** was also achieved using solvent-drop grinding and slurry methods.

A TDF cocrystal screen using pharmaceutically acceptable carboxylic acids was also performed given that alcohols and carboxylic acids are both capable of serving as hydrogen bond donors.[31] TDF and hydrocinnamic acid (HCA) were cocrystallized from an acetonitrile solution in a 1 : 1 molar ratio. Successful preparation of TDF:HCA cocrystals (**3**) were also obtained through solvent-drop grinding and slurry methods. The crystal structure of **3** was determined by single crystal X-ray diffraction. **3** adopts a similar supramolecular arrangement compared to that of **1** and **2** and is found to exhibit similar unit cell parameters in $P2_1$. The asymmetric unit of **3** comprises one TDF and one HCA molecule and no proton transfer is evident from the bond lengths. TDF supramolecular chains linked *via* N–H···O=C hydrogen bonds [N3-H3···O5: N···O 2.918(3) Å, H···O 2.05 Å, N–H···O 168.3°] are reminiscent of **1** and **2**. HCA molecules are linked to the TDF chains through OH···O=C hydrogen bonds [O1-H1···O6: O···O 2.748(3) Å, O H···1.94 Å, O–H···O 160.3°]. The assemblies of the TDF chains with pendant HA molecules are once again interdigitated as presented in Fig. 5. The interdgitation is supported by the edge-to-face $C–H_{arom}···\pi$ interactions between HA and TDF molecules.

We further investigated the generality of these hydrogen bonding patterns by looking at cocrystals of 4-hydroxybenzoic acid (HBA) and TDF. From a crystal engineering viewpoint, HBA is a coformer with higher molecular complexity because both its hydroxyl and carboxylic acid groups can act as hydrogen bond donors. Cocrystals of TDF and HBA (**4**) were obtained from both solution and grinding. However, we have been unable to obtain

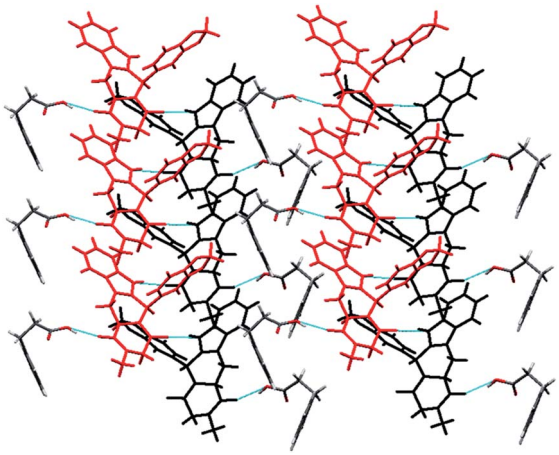

Fig. 5 Crystal packing of **3**.

suitable crystals of **4** for single crystal X-ray diffraction analysis to date. In the absence of a single crystal structure of **4**, its PXRD profile was compared against that of **1**–**3**. As presented in Fig. 6, the PXRD profile of **4** was found to be distinctly different from that of the other TDF cocrystals. However, this is by no means sufficient to draw any conclusions about the nature of the supramolecular interactions that occur in **4**. The unit cell parameters of **4**, obtained from indexing the PXRD data,[32] were also found to be different from that of **1**, **2** and **3**.

In conclusion, TDF was successfully cocrystallized with three pharmaceutically acceptable coformers, MPB, PPB and HCA, through both solution and grinding methods. The structures of three resulting cocrystals (**1**, **2** and **3**) were determined by X-ray diffraction techniques. In all three cocrystals, TDF molecules are observed to be linked by N–H···O hydrogen bonds that form the same supramolecular chains seen in pure TDF. However, when a coformer with higher molecular complexity, HBA, was cocrystallized with TDF, there are significant changes in the PXRD profile. Future work will focus upon determination of the crystal structure of **4** and cocrystal screening with a broader range of coformers. The resulting series of TDF cocrystals will be evaluated using *in vitro* and *in vivo* studies.

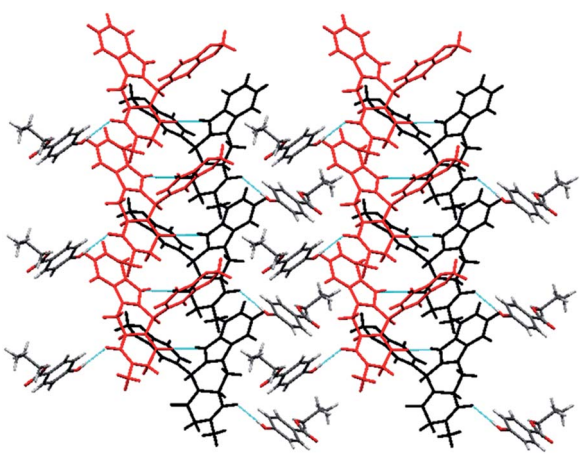

Fig. 4 Crystal packing of **2**.

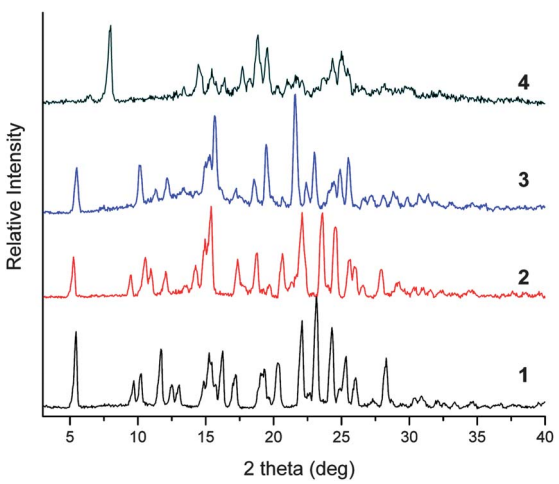

Fig. 6 PXRD profiles for **1**–**4**.

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Notes and references

‡ *Crystal data* for **1–3**:
1: $C_{30}H_{27}N_3O_7$, $M = 541.55$, monoclinic, $a = 9.4455(3)$ Å, $b = 7.8767(2)$ Å, $c = 17.2532(5)$ Å, $\beta = 98.352(2)^\circ$, $U = 1270.01(6)$ Å^3, $T = 100(2)$K, space group $P2_1$, $Z = 2$, $D_c = 1.416$ gcm^{-3}, $\mu = 0.844$ mm^{-1}, $F(000) = 568$, 3531 unique ($R_{int} = 0.0292$), Final $R1$ ($wR2$) = 0.0349 (0.0864) [$I > 2.0\ \sigma(I)$].
2: $C_{32}H_{31}N_3O_7$, $M = 569.60$, monoclinic, $a = 9.3357(2)$ Å, $b = 8.3056(2)$ Å, $c = 17.3542(5)$ Å, $\beta = 90.854(2)^\circ$, $U = 1345.47(6)$ Å^3, $T = 100(2)$K, space group $P2_1$, $Z = 2$, $D_c = 1.406$ gcm^{-3}, $\mu = 0.824$ mm^{-1}, $F(000) = 600$, 6565 reflections measured, 3487 unique ($R_{int} = 0.0358$), Final $R1$ ($wR2$) = 0.0410 (0.0963) [$I > 2.0\ \sigma(I)$].
3: $C_{31}H_{29}N_3O_{6,}$ $M = 539.57$, monoclinic, $a = 9.548(1)$ Å, $b = 8.188(1)$ Å, $c = 16.673(2)$ Å, $\beta = 96.305(9)^\circ$, $U = 1295.5(3)$ Å^3, $T = 100(2)$K, space group $P2_1$, $Z = 2$, $D_c = 1.383$ gcm^{-3}, $\mu = 0.795$ mm^{-1}, $F(000) = 568$, 8513 reflections measured, 3654 unique ($R_{int} = 0.0439$), Final $R1$ ($wR2$) = 0.0420 (0.0957) [$I > 2.0\ \sigma(I)$].

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32 The indexing of the laboratory PXRD data of **4** was performed by the DICVOL04 program (Boultif *et al.*, J. Appl. Cryst., 2004, 37, 724–731). The structure of **4** was determined in the monoclinic crystal system with unit cell parameters reported as $a = 16.223(18)$ Å, $b = 6.117(7)$ Å, $c = 11.085(12)$ Å and $\beta = 94.39(12)^\circ$.

