Crystal engineering of pharmaceutical co-crystals from polymorphic active pharmaceutical ingredients†

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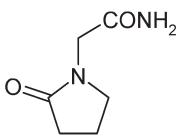
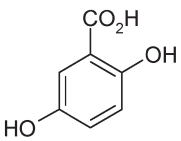
The carboxylic acid–primary amide supramolecular heterosynthon is exploited for the generation of pharmaceutical co-crystals that contain two active pharmaceutical ingredients that are polymorphic in their pure forms.

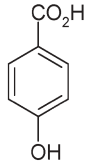
That crystal engineering has matured into a form of supramolecular synthesis is the consequence of several decades of research focused upon gaining a better understanding of the forces that sustain and direct crystal structures.[1] The fundamental precept of crystal engineering is that crystals are in effect "supermolecules",[2] the result of a series of directional, and therefore predictable, molecular recognition events or supramolecular synthons.[3] A salient feature of crystal engineered structures is that they are designed from first principles and can therefore consist of a diverse range of chemical components as exemplified by coordination polymers (*i.e.*, metals and organic ligands),[4] polymers sustained by organometallic linkages[5] and hydrogen bonded organic networks.[1d,e,6] Active pharmaceutical ingredients, APIs, are extremely valuable materials so it is perhaps surprising that crystal engineering has only recently addressed APIs *via* development of a fourth class of API, pharmaceutical co-crystals.[7] Whereas co-crystals have long been known as *addition compounds*[8] or *organic molecular compounds*[9] the Cambridge Structural Database, CSD,[10] indicates that they remain relatively unexplored with very few entries prior to 1960 and even now there are only *ca.* 1450 hydrogen bonded co-crystals *vs.* almost 35,000 hydrates. The potential benefits of co-crystals include the generation of novel NLO materials,[11] solvent-free organic synthesis,[12] modification of photographic films[13] and formulation of APIs,[7,14] which is the focus of this contribution.



Piracetam, **1**



Gentisic acid, **2**



p-Hydroxybenzoic acid, **3**

Pharmaceutical co-crystals, *i.e.*, co-crystals that are formed between an API and a co-crystal former that is a solid under ambient conditions, represent a new paradigm in API formulation that might address important intellectual and physical property issues in the context of drug development and delivery. In this contribution we demonstrate how the carboxylic acid–primary amide supramolecular heterosynthon[7c] can be exploited to generate pharmaceutical co-crystals of a polymorphic API, piracetam, **1**,[15] in which the co-crystal formers are also polymorphic and APIs in their own right: gentisic acid, **2**,[16] and *p*-hydroxybenzoic acid, **3**.[17]

Piracetam, (2-oxo-1-pyrrolidinyl)acetamide, **1**, is a nootropic drug that works to boost intelligence by stimulating the central nervous system.[18] Four polymorphic forms of **1** have been reported[15] although only three, refcode BISMEV, have been deposited in the CSD. No co-crystals, solvates or hydrates have been reported although one study suggests that **1** may exhibit as many as 6 polymorphs.[19] Gentisic acid, 2,5-dihydroxybenzoic acid, **2**, is an aspirin metabolite that exhibits NSAID activity.[20] Gentisic acid exhibits two polymorphic forms[21] and forms co-crystals with piperazine-2,5-dione and L-proline.[22] Single crystals of the 1:1 co-crystal of piracetam and gentisic acid, **4**, were obtained *via* slow evaporation from acetonitrile. Co-crystal **4** can also be prepared *via* grinding or slurrying in water. Co-crystal **4** was characterized by IR, melting point, DSC, PXRD and single crystal X-ray diffraction.[23] The carboxylic acid–amide supramolecular heterosynthon has been long documented[24] and 71 of the 153 structures in the CSD that contain both a carboxylic acid and a primary amide are sustained by this interaction. It would therefore be unsurprising if the acid–amide supramolecular heterosynthon were to occur in **4** and, as revealed by Fig. 1a, this is indeed the case. The remaining H-bond donors are satisfied as follows: the 2-hydroxy group of gentisic acid forms an intramolecular hydrogen bond and acts an acceptor to the *anti*-oriented NH of the primary amide; the 5-hydroxy group of gentisic acid serves as a hydrogen bond donor to the ring carbonyl of piracetam (Fig. 1b). The resulting network exhibits 4,4-topology and it is 2-fold interpenetrated (Fig. 1c).

Piracetam also forms a 1:1 co-crystal with *p*-hydroxybenzoic acid, **5**. Co-crystal **5** can be crystallized from acetonitrile *via* slow evaporation. Co-crystal **5** can also be prepared *via* grinding or slurrying in water. The crystal structure of **5**[25] reveals the presence of the acid–amide supramolecular heterosynthon which in turn dimerizes to form a tetrameric motif sustained by N–H···O hydrogen bonding (Fig. 2). This tetrameric motif is found in 10 (14%) of the 71 structures in the CSD that contain acid–amide supramolecular heterosynthons.[26] The ring carbonyl of piracetam molecules and the hydroxy group of **3** H-bond each tetramer to four others, thereby affording a 3-fold interpenetrated network.

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† Electronic supplementary information (ESI) available: Experimental details of solvent drop grinding, PXRD spectra and interpenetration in **5**. See http://dx.doi.org/10.1039/b501304f

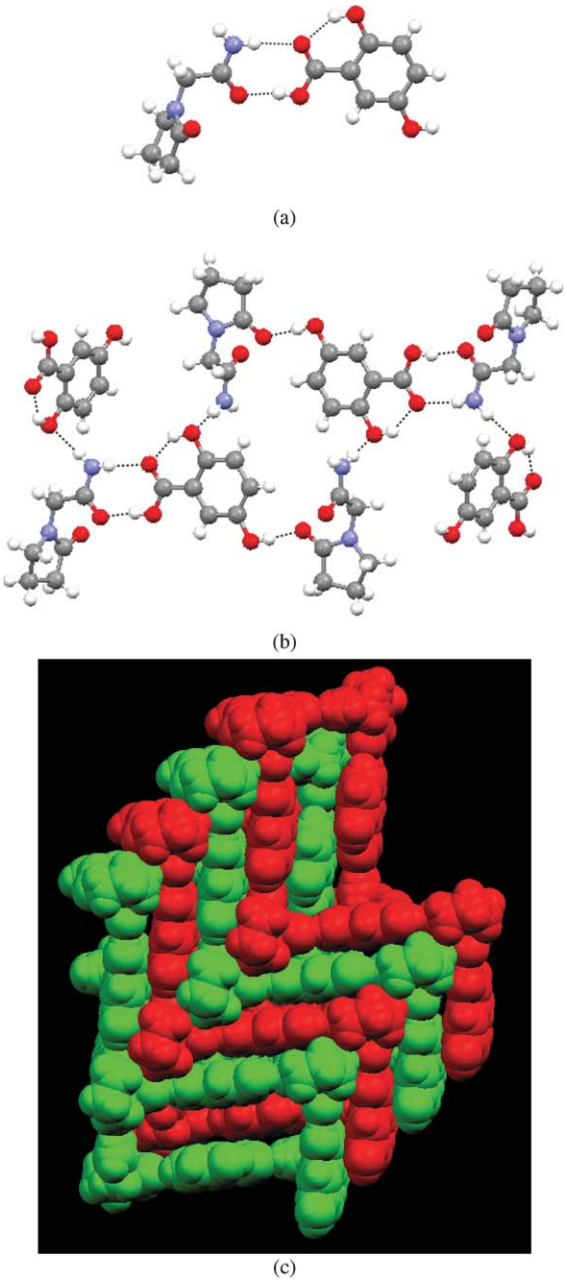

Fig. 1 (a) The carboxylic acid–amide supramolecular heterosynthon in the 1:1 co-crystal of piracetam and gentisic acid, **4**. Structural parameters: O–H_{acid}···O = 2.590(15) Å, N–H_{syn}···O = 2.907(18) Å, N–H_{anti}···O = 2.944(19) Å. (b) A portion of the hydrogen bond network in **4**. (c) A space-filling model of the 2-fold interpenetration that occurs in **4**.

That APIs are promiscuous in the context of polymorphism is a critical issue for the pharmaceutical industry:[27] from a regulatory perspective it has been established that bioactivity can change between forms; from an intellectual property perspective, polymorphic forms are established in law as discrete materials and new forms can be patented. We have therefore investigated the general occurrence of polymorphism in existing co-crystals. A CSD search revealed only eleven examples of polymorphism in hydrogen bonded co-crystals for which coordinates are available for two or more forms.[28] Interestingly, the polymorphism in these eleven co-crystals can be attributed to conformational flexibility or different

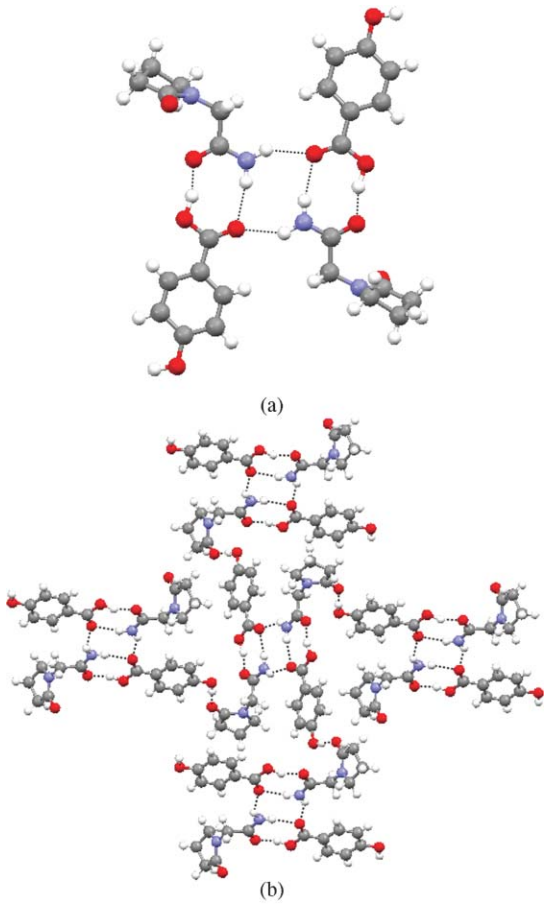

Fig. 2 (a) The carboxylic acid–amide supramolecular heterosynthon in the tetrameric motif that sustains **5**. Structural parameters: O–H_{acid}···O = 2.598(3)Å, N–H_{syn}···O = 2.955(3) Å, N–H_{anti}···O = 2.908(3) Å. (b) A portion of the hydrogen bond network in **5**.

packing between layers, *i.e.*, the hydrogen bonded supramolecular synthons are consistent. Co-crystals **4** and **5** were therefore screened for the existence of polymorphs using solvent-drop grinding, a technique that has been shown to be able to generate and control polymorphism.[29] Mechanical grinding experiments were conducted in reaction vessels by adding gentisic acid or *p*-hydroxybenzoic acid to solid piracetam form A. A group of 23 solvents (water, acetone, methanol, ethanol, ethyl acetate, *n*-hexane, toluene, acetonitrile, tetrahydrofuran, isopropyl acetate, benzyl alcohol, nitromethane, dimethyl amine, 2-butanol, ethyl formate, acetic acid, methyl ethyl ketone, methyl *tert*-butyl ether, chlorobenzene, *N*-methyl pyrrolidone, 1,2-dichloroethane, dimethyl sulfoxide and dimethoxyethane) was evaluated by adding a different solvent to each well. The samples were ground for 20 minutes and characterized using powder X-ray diffraction. Co-crystals **4** and **5** were also obtained by slurrying 0.62 mmol of piracetam and 0.62 mmol of gentisic acid or *p*-hydroxybenzoic acid in water (100μL) for 60 or 16 hours, respectively. Co-crystals **4** or **5** were obtained from all grinding and slurrying reactions as a mixture with one or both of the starting materials, *i.e.*, co-crystals **4** and **5** do not exhibit polymorphism based on a series of solvent-mediated grinding experiments (See ESI for experimental details and PXRD spectra†).

In summary, we address herein the use of supramolecular heterosynthons, in particular the carboxylic acid–primary amide

dimer, to crystal engineer pharmaceutical co-crystals from pairs of APIs that are polymorphic in their pure forms. An analysis of the CSD and evaluation of new pharmaceutical co-crystals suggests that these co-crystals are robust enough to be prepared *via* solution, slurry or solid-state methods and that they appear to be less prone to polymorphism than the corresponding single component APIs. However, it should be stressed that the amount of data available concerning the extent of polymorphism in co-crystals remains minimal and that one will not be able to make definitive conclusions even if exhaustive high throughput screenings are conducted.

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‡ See http://dx.doi.org/10.1039/b501304f for crystallographic data in CIF or other electronic format.

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23 Crystal data for **4**: $C_{13}H_{16}N_2O_6$, $M = 296.28$, monoclinic, $a = 27.896(3)$, $b = 5.1762(5)$, $c = 19.7879(18)$ Å, $\beta = 101.090(2)^\circ$, $V = 2803.9(4)$ Å^3, $T = 100$ K, space group $C2/c$, $Z = 8$, $\rho_{calc} = 1.404$ g cm^{-3}, μ(Mo-K$_\alpha$) = 0.112 mm^{-1}, 7622 reflections measured, 2873 unique reflections, 2417 observed reflections [$I > 2\sigma(I)$], R_1 obs = 0.043, wR_2 obs = 0.108. CCDC 262605.‡ Microcrystals of **4** can also be obtained by grinding **1** and **2** in a 1:1 ratio for four minutes in a ball mill or by melting the two components.

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25 Crystal data for **5**: $C_{13}H_{16}N_2O_5$, $M = 280.28$, monoclinic, $a = 14.780(3)$, $b = 5.5029(12)$, $c = 17.068(4)$ Å, $\beta = 109.557(4)^\circ$, $V = 1308.0(5)$ Å^3, $T = 100$ K, space group $P2_1/n$, $Z = 4$, $\rho_{calc} = 1.423$ g cm^{-3}, μ(Mo-K$_\alpha$) = 0.11 mm^{-1}, 4995 reflections measured, 2220 unique reflections, 1753 observed reflections [$I > 2\sigma(I)$], R_1 obs = 0.048, wR_2 obs = 0.109. CCDC 262606.‡ Microcrystals of **5** can also be obtained by grinding **1** and **3** in a 1:1 ratio for four minutes in a ball mill or by melting the two components.

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