Development of a pharmaceutical cocrystal of a monophosphate salt with phosphoric acid†

Alex M. Chen,*[a] Martha E. Ellison,*[a] Andrey Peresypkin,[a] Robert M. Wenslow,[a] Narayan Variankaval,[a] Cecile G. Savarin,[a] Theresa K. Natishan,[a] David J. Mathre,[a] Peter G. Dormer,[a] Danielle H. Euler,[b] Richard G. Ball,[a] Zhixiong Ye,[a] Yaling Wang[a] and Ivan Santos[a]

Received (in Austin, TX, USA) 29th August 2006, Accepted 20th October 2006
First published as an Advance Article on the web 1st November 2006
DOI: 10.1039/b612353h

We report the first case of a pharmaceutical cocrystal formed between an inorganic acid and an active pharmaceutical ingredient (API), which enabled us to develop a stable crystalline and bioavailable solid dosage form for pharmaceutical development where otherwise only unstable amorphous free form or salts could have been used.

Crystal engineering of cocrystals involving active pharmaceutical ingredients (APIs) has been the subject of increased interest.[1–3] Pharmaceutical cocrystals, defined as hydrogen-bonded complexes between APIs and a solid component, have represented a relatively unexplored class of compounds. The engineering of cocrystals promises a new approach for the development of suitable solid forms of drug substances, particularly when amorphous material is undesirable and bioavailable crystalline free forms (acids, bases, neutral forms) or salts are not attainable. A classic example has been reported by Remenar *et al.* who have shown that formation of cocrystals of a triazole drug with 1,4-dicarboxylic acids led to significant improvement in the solubility of the drug.[2] Likewise, Variankaval *et al.* have recently reported the formation of variable stoichiometry L-tartaric acid cocrystals of the phosphodiester-IV Inhibitor demonstrating >20-fold improvement in drug plasma concentrations as compared to a neutral form.[3] Despite the significant growth of publications in the area of pharmaceutical cocrystals, all reported pharmaceutical cocrystals were formed between organic acids or bases and the API. Although a search of the Cambridge Structural Database (CSD)[4] and literature[5] revealed several examples of cocrystal formation between an inorganic acid and a solid compound, the cocrystal engineering approach using inorganic acid as a cocrystal former has been surprisingly neglected in the area of pharmaceutical cocrystal development. Moreover, among all pharmaceutical cocrystals reported, most involved an API that had been marketed as an amorphous form, as a crystalline free form, or as a salt form. Of these, only a few were directly developed and selected as the optimal solid dosage form during pharmaceutical development.[3,6]

In this contribution, we report the first case of a pharmaceutical cocrystal formed between an inorganic acid and an API monophosphate salt. More importantly, we demonstrated that the cocrystal shows excellent physicochemical properties and adequate bioavailability and was directly selected as the optimal solid dosage form during pharmaceutical development where otherwise only unstable amorphous free form or salts could have been used. Specifically, we developed a novel pharmaceutical cocrystal of a monophosphate salt of an API and phosphoric acid in which one phosphoric acid is bound to the API by transfer of a proton to an amine group while the other is hydrogen-bonded to the API *via* a strong O–H···O=C hydrogen bond. The two crystallographically inequivalent phosphoric acid molecules are also hydrogen-bonded to each other and form a helix with a pitch equal to the length of the *b* axis, which appears to be important for the crystal packing. It should be noted that since phosphoric acid exists as a solid under ambient conditions, the reported complex is formed between the two solid components and thus is named a cocrystal rather than a solvate.[1]

Compound **I** was a development candidate for oral administration (Fig. 1). The compound has two pK_a values with 8.3 for N-1 and 2.7 for N-3 as determined by potentiometric titration. Initially, an amorphous bis-HCl salt was used for early development. However, the amorphous bis-HCl salt was hygroscopic and chemically unstable, exhibiting 7 and 40% degradation after one week at 40 and 80 °C/ambient relative humidity (RH) respectively and therefore was unsuitable for further development. Furthermore, efforts to obtain a crystalline form of the free base were unsuccessful. Therefore, extensive efforts were undertaken to form crystalline salts. Given the high pK_a of 8.3 for the first nitrogen, N-1, an initial high throughput (HT) salt screening was performed by adding one equivalent of numerous

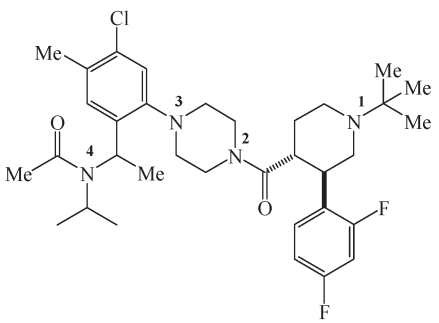

Fig. 1 Molecular structure of compound **I**.

[a] *Merck & Co. Inc., P.O. Box 2000, Rahway, New Jersey, 07065, USA. E-mail: alex_chen2@merck.com; martha_ellison@merck.com; Fax: +1 732 594 9140; Tel: +1 732 594 1599*
[b] *Merck & Co. Inc., P.O. Box 4, West Point, PA, 19486, USA*

† Electronic supplementary information (ESI) available: Crystallographic data of cocrystal, overlay of the calculated XRPD pattern based on single crystal structure and the capillary XRPD pattern of powder samples of cocrystal, liquid NMR data and experimental conditions. See DOI: 10.1039/b612353h

pharmaceutically acceptable organic and inorganic acids to the free base and then the crystallizations were performed by evaporation and cooling in combinations of solvent mixtures.

As a result of the HT salt screening, the only crystalline form produced was with phosphoric acid. By ICP analysis and base-titration, this crystalline form was determined to consist of two moles of phosphoric acid per mole of compound **I** (compound **I**·$2H_3PO_4$). Compound **I**·$2H_3PO_4$ was further characterized by XRPD, DSC, TGA, and determined to be anhydrous. As a rule of thumb, a pK_a difference of at least two units between base and acid is needed to form a salt. Given that the second pK_a of compound **I** is 2.7 and the lowest pK_a of phosphoric acid is 2.1, the formation of the bisphosphate salt is therefore not favored. This led to our hypothesis that the second phosphoric acid was possibly bound by hydrogen-bonding and we formed a cocrystal of a monophosphate salt with phosphoric acid.

In an effort to elucidate the structure information and prove our hypothesis that N-3 was not protonated by the second phosphoric acid, solution and solid state NMR (SSNMR) experiments were employed. A ^{15}N solution NMR experiment was first performed on compound **I**·$2H_3PO_4$ *via* ^{1}H–^{15}N HMBC to obtain chemical shift and assignments.‡ Then two ^{15}N SSNMR experiments were performed on compound **I**·$2H_3PO_4$ with the spectra displayed in Fig. 2. The long contact time experiment yielded signals for all nitrogen sites on the molecule. Chemical shift assignments were made by correlation to solution NMR data. The short contact time experiments yielded increased signal intensity for nitrogen sites with close approaching protons. The short contact time spectrum for compound **I**·$2H_3PO_4$ displays intensity for only N-1, indicating significantly stronger proton coupling for N-1 compared to N-2, N-3, and N-4. These data suggest protonation only occurs at N-1 for compound **I**·$2H_3PO_4$ in the solid state and the crystalline compound **I**·$2H_3PO_4$ which consists of two moles of phosphoric acid per mole of compound **I** is likely a cocrystal of a monophosphate salt and phosphoric acid.

The cocrystal formation was further confirmed by single crystal X-ray diffraction.§¶ The calculated XRPD pattern based on a single crystal structure conforms to the capillary XRPD pattern of powder samples. The single crystal crystallizes in the $P2_1$ space group with one molecule of compound **I** and two molecules of phosphoric acid in the asymmetric unit [Fig. 3(a)]. The single crystal structure shows the expected proton transfer from the acid to the piperidyl nitrogen (N-1) with a pK_a of 8.3. In addition, the structure also reveals an uncommon specific interaction between a second phosphoric acid and the carbonyl of the amide group, suggestive of a possible new motif for cocrystal formation. This interaction is possible since the other carbonyl already participates in a hydrogen-bond with the ionized phosphoric acid making the amide carbonyl the only remaining strong hydrogen-bond acceptor in the lattice. More interestingly, the two crystallographically inequivalent phosphoric acid molecules are hydrogen-bonded to each other [Fig. 3(b)] and form a helix with a pitch equal to the length of the *b* axis (10.995 Å). Detailed images of the hydrogen-bonding motif are provided in the ESI.† This chain of hydrogen-bonded phosphoric acid units appears to be important for crystal packing and probably explains the formation of the cocrystal during the HT salt screening where only one equivalent of phosphoric acid was added.

The physicochemical properties of this cocrystal have been fully characterized. The cocrystal displays a high melting point of *ca.* 235 °C, plate-like morphology, and good powder flow properties. Excellent chemical and physical stability was observed with no detectable degradation or form change at 40 °C/75% RH and 60 °C after eight weeks of storage. Moreover, the cocrystal is highly soluble in water (>250 mg mL^{-1}) and exhibited excellent *in vivo* performance. Additionally, HT polymorph screening of the monophosphate salt and of the cocrystal of the monophosphate salt with phosphoric acid did not yield any new crystalline forms.

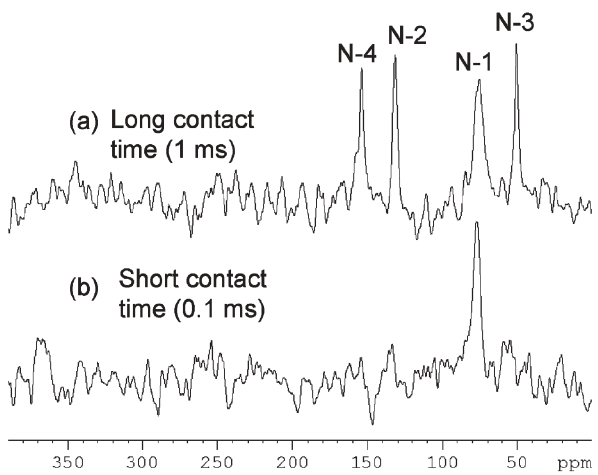

Fig. 2 ^{1}H–^{15}N CPMAS SSNMR spectra of compound **I**·$2H_3PO_4$ performed at (a) 1 ms and (b) 0.1 ms contact time.

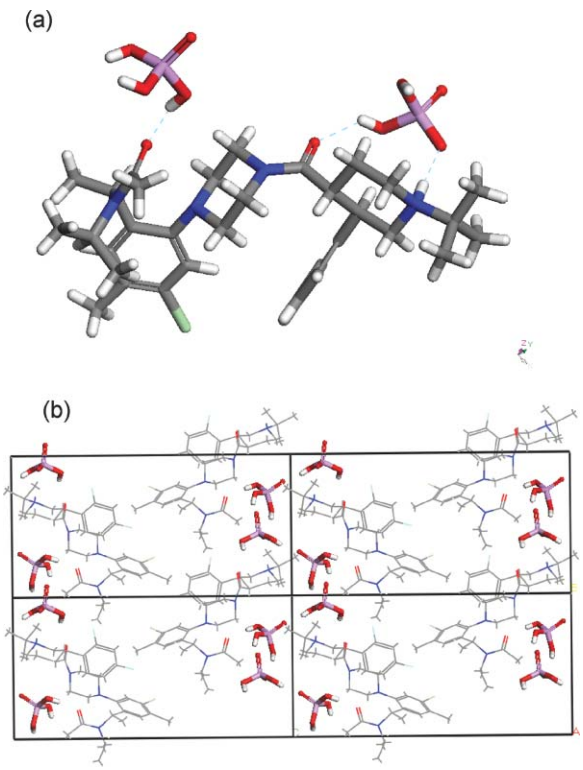

Fig. 3 (a) Asymmetric unit of the cocrystal of the compound **I** monophosphate salt with phosphoric acid; (b) structure showing the proximity and hydrogen-bonding of the two inequivalent phosphoric acid molecules in the crystal lattice.

Based on its superior physicochemical properties, this cocrystal was therefore chosen as the optimal solid form of compound **I** for further development.

In conclusion, a novel pharmaceutical cocrystal of the compound **I** monophosphate salt with phosphoric acid was developed and selected as the optimal candidate for pharmaceutical development as a direct result of an extensive solid form selection process. The formation of the cocrystal enabled us to develop a stable crystalline and bioavailable solid form for pharmaceutical development where otherwise only unstable amorphous free base or salts could have been used. This is the first case of a pharmaceutical cocrystal formed between a monophosphate salt of an API and phosphoric acid. Our report suggests that a pharmaceutical cocrystal engineering approach using an inorganic acid such as phosphoric acid as a cocrystal former can be explored to develop suitable solid dosage forms for pharmaceutical development. In cases where crystalline solid forms are preferred and routine screening efforts fail to provide suitable crystalline free forms or salts, a possible cocrystal formation between an inorganic acid and an API may provide a suitable solution, as demonstrated in our report.

We thank Kara Rubin for performing the HT screening experiments, Tiebang Wang for the ICP analysis.

Notes and references

‡ ^{15}N solution NMR experiments were performed on *ca.* 20 mg mL^{-1} solutions of compound **I**·2H_3PO_4 in methanol-d_4 at −30 °C.

§ Single crystal was grown by slow evaporation of a saturated solution of compound **I**·2H_3PO_4 in 2 : 1 (v/v) methanol–H_2O at room temperature.

¶ Crystal data: $C_{34}H_{53}Cl\ F_2N_4O_{10}P_2$, M_r = 813.190, monoclinic, $P2_1$, a = 8.901(5), b = 10.995(6), c = 21.876(12) Å, β = 100.157(9)°, V = 2107.3(19) Å^3, Z = 2, D_x = 1.282 g cm^{-3}, monochromatized radiation λ(Mo) = 0.71073 Å, μ = 0.23 mm^{-1}, F(000) = 860, T = 298° K. Data were collected on a Bruker CCD diffractometer to a θ limit of 26.46° which yielded 20 016 reflections. There are 8502 unique reflections with 6714 observed at the 2σ level; R_{int} = 0.050. The final agreement statistics are: R = 0.098 [based on 6714 reflections with $I > 2\sigma(I)$], wR = 0.224, S = 1.18 with $(\Delta/\sigma)_{max}$ = 0.01. CCDC 619263. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b612353h.

1 G. Bettinetti, M. R. Caira, A. Callegari, M. Merli, M. Sorrenti and C. Tadini, *J. Pharm. Sci.*, 2000, **89**, 478–489; I. D. H. Oswald, D. R. Allan, P. A. McGregor, W. D. S. Motherwell, S. Parsons and C. R. Pulham, *Acta Crystallogr., Sect. B*, 2002, **58**, 1057–1066; B. D. B. Walsh, M. W. Bradner, S. Fleischman, L. A. Morales, B. Moulton, N. Rodriguez-Hornedo and M. J. Zaworotko, *Chem. Commun.*, 2003, 186–187; O. Almarsson and M. J. Zaworotko, *Chem. Commun.*, 2004, 1889–1896; S. L. Childs, L. J. Chyall, J. T. Dunlap, V. N. Smolenskaya, B. C. Stahly and G. P. Stahly, *J. Am. Chem. Soc.*, 2004, **126**, 13 335–13 342; A. V. Trask, W. D. S. Motherwell and W. Jones, *Cryst. Growth Des.*, 2005, **5**(3), 1013–1021; P. Vishweshwar, J. A. McMahon, M. L. Peterson, M. B. Hickey, T. R. Shattock and M. J. Zaworotko, *Chem. Commun.*, 2005, 4601–4603; J. A. McMahon, J. A. Bis, P. Vishweshwar, T. R. Shattock, O. L. McLaughlin and M. J. Z. Zaworotko, *Z. Kristallogr.*, 2005, **220**, 340–350; P. M. Bhatt, N. V. Ravindra, R. Banerjee and G. R. Desiraju, *Chem. Commun.*, 2005, 1073–1075; R. Vishweshwar, J. A. Mcmahon, J. A. Bis and M. J. Zaworotko, *J. Pharm. Sci.*, 2006, **95**(3), 499–516; L. S. Reddy, N. J. Babu and A. Nangia, *Chem. Commun.*, 2006, 1369–1371.

2 J. F. Remenar, S. L. Morissette, M. L. Peterson, B. Moulton, J. M. MacPhee, H. R. Guzman and O. Almarsson, *J. Am. Chem. Soc.*, 2003, **125**, 8456–8457.

3 N. Variankaval, R. Wenslow, J. Murry, R. Hartman, R. Helmy, E. Kwong, S. Clas, C. Dalton and I. Santos, *Cryst. Growth Des.*, 2006, **6**(3), 690–700.

4 CSD refcodes: HAKDED, HISTPA, IZOWID, TODNUV, VEGKIB, WAVHOQ, YEMJIJ.

5 R. H. Blessing, *Acta Crystallogr., Sect. B*, 1986, **42**, 613; R. V. G. Sundera-Rao, J. W. Turley and R. Pepinsky, *Acta Crystallogr.*, 1957, **10**, 435–436.

6 A. W. Newman and G. P. Stahly, *Drugs Pharm. Sci.*, 2002, **117**, 1–57.