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Using Cocrystals To Systematically Modulate Aqueous Solubility and Melting Behavior of an Anticancer Drug

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During the development and formulation of any active pharmaceutical ingredient (API) that is to be delivered in a solid form, a wide range of stringent performance parameters (e.g., solubility, dissolution rate, thermal stability, etc.) needs to be carefully considered.[1] It is thus not surprising that poor biopharmaceutical properties (as opposed to toxicity or lack of efficacy)[2] are the main reason that less than 1% of active compounds eventually make it into the marketplace.[3] Solubility remains a key issue,[4] and a number of approaches for addressing this problem have been pursued, such as micronization,[5] the use of salt forms,[6] and solubilization in cosolvents[7] and micellar solutions.[8−10] Although these techniques can be effective, there is a need for a broader range of solid forms from which to choose a particular API in order to optimize physicochemical properties without tampering with the molecule itself.

Recent advances in crystal engineering[11] have enabled the design of cocrystals in which two or more molecular compounds are incorporated within the same crystalline lattices in specific stoichiometric amounts.[12] Cocrystal synthesis does not involve making/breaking of covalent bonds, and it may therefore be possible to fine-tune physical properties by exercising precise control over the supramolecular assembly, since the crystal structure determines the resulting physical properties of the compound. For example, the melting points of even-numbered aliphatic dicarboxylic acids decrease monotonically with increasing number of methylene groups in the chain; the structural consistency among the five compounds shown in Figure 1 translates to a predictable relationship between molecular structure and physical behavior. The melting points of odd-numbered diacids also decrease with an increase in the number of methylene groups, but they have significantly lower melting points than their even-numbered analogues as a result of significant differences in crystal structure/packing.[13]

Against this background, we hypothesized that if we can incorporate an API within a series of crystalline solids characterized by considerable structural consistency, we may be able to fine-tune melting points and aqueous solubility. Changes to the physical properties could be achieved by varying the cocrystallizing agents in a systematic fashion without altering the precise nature of the molecular recognition events that drive the supramolecular assembly.

Herein we present a systematic structure−property study of a series of cocrystals of hexamethylenebisacetamide **A**, a compound that is capable of inhibiting the proliferation of lung cancer cells and is also being used in the treatment of myelodysplastic syndrome and resistant acute myelogenous leukemia.[14] Our strategy was to synthesize infinite API···diacid···API···diacid chains using the well-known COOH···py hydrogen-bond-based synthon,[15] and these chains were subsequently going to be arranged into two-dimensional (2D) layers as a result of API-based self-complementary amide···amide hydrogen bonds.[16] All of the diacids used in this study are generally regarded as safe by the FDA. The main objectives of this study were (i) to determine whether we could synthesize a series of cocrystals with the desired structural consistency; (ii) to establish how well the melting point of the cocrystal can be correlated with the nature of the cocrystallizing agent; and (iii) to establish how well the solubility can be correlated with the nature of the cocrystallizing agent.

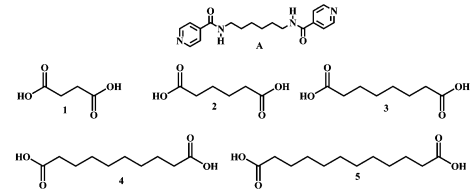

Figure 1. Target API and dicarboxylic acids.

Table 1. Comparison of Structural Data

	A1	A2	A3	A4	A5
a (Å)	5.1754(4)	5.1412(4)	5.1392(5)	5.1506(4)	5.1519(4)
b (Å)	10.9294(8)	5.2394(4)	5.2412(5)	5.2481(4)	5.2778(5)
c (Å)	10.9423(8)	21.396(2)	23.145(2)	24.521(2)	26.148(3)
α (deg)	118.826(4)	95.094(5)	94.050(3)	89.647(4)	86.023(6)
β (deg)	91.381(5)	95.603(4)	95.222(2)	87.252(4)	89.386(6)
γ (deg)	99.872(4)	91.076(5)	91.277(2)	88.505(5)	88.496(6)
V (Å^3)	530.11(7)	571.10(8)	619.0(1)	661.82(8)	709.0(1)

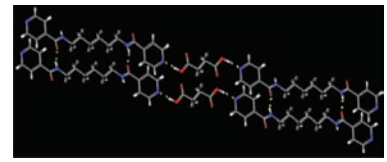

Figure 2. 2D sheet in the structure of **A1** generated through O−H···N and N−H···O hydrogen bonds.

Cocrystallization reactions between **A** and **1**−**5** were carried out, and IR spectroscopy was used to screen all of the resulting solids for cocrystal formation. We were also able to grow crystals suitable for single-crystal X-ray diffraction of all products (see the Supporting Information). A summary of the unit cell parameters for the crystal structures of **A1**−**A5** is given in Table 1. As shown by the structural parameters, the five cocrystals are isostructural, and the increase in unit cell volume is a reflection of an increase in the size of the cocrystallizing agent. Because of the close structural similarities, only two structures are shown.

In **A1** (the 1:1 cocrystal of **A** and **1**), a primary O−H···N interaction between the pyridyl moiety and the carboxylic acid was observed [O31···N11, 2.7094(19) Å], resulting in 1D chains that in turn are organized into layers via interchain N−H···O hydrogen bonds [N17···O17, 2.9902(19) Å] (Figure 2). Similar structures were obtained with longer-chain acids, as shown by **A4**, in which an O−H···N hydrogen bond between the pyridyl moiety and the carboxylic acid [O31···N11, 2.6690(11) Å] was observed. The crystal

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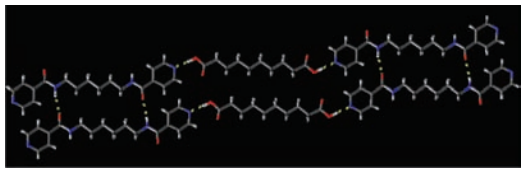

Figure 3. 2D sheet in **A4** generated through O−H···N and N−H···O hydrogen bonds.

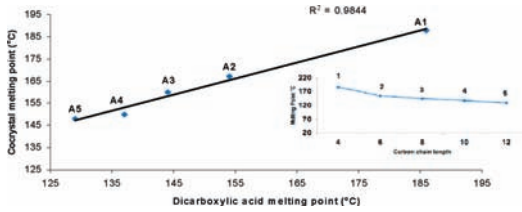

Figure 4. Melting points for **A1**−**A5** plotted vs the melting points for the corresponding diacids **1**−**5**. The equation for the fitted line is $y = 0.72x + 54$. The inset shows the melting points of **1**−**5** as a function of carbon chain length.

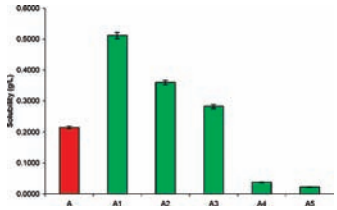

Figure 5. Aqueous equilibrium solubilities of **A** and **A1**−**A5.**

structure also contains 2D layers generated via self-complementary amide···amide N−H···O hydrogen bonds [N17···O17, 3.0127(14) Å) (Figure 3).

Having achieved the required structural consistency, we subsequently examined whether the thermal behavior of these cocrystals could be correlated with any molecular feature of the five cocrystallizing agents (Figure 4). The data clearly show that the melting points of these five crystalline solids are directly related to the melting points in the dicarboxylic acids. The highest-melting cocrystal contains the dicarboxylic acid with the highest melting point, and the lowest-melting acid produces the lowest melting cocrystal; this demonstrates that the melting behavior of the five solid forms of this API can be modulated in a predictable manner over a considerable range (148−188 °C; the melting point of the API itself is 181−182 °C).

Although thermal properties are an important issue, solubility is a key factor, so we also determined the aqueous equilibrium solubilities of **A1**−**A5** (Figure 5). The results show that the aqueous solubility of **A** can in fact be improved by a factor of 2.5 without altering the molecular structure of the API itself. Although the solubilities of the five cocrystals of the API did not produce a linear correlation as did the melting points, the trend in physicochemical properties of the cocrystals can certainly be rationalized in terms of the aqueous solubilities of the dicarboxylic acids. The cocrystals of the longer-chain diacids, which are less polar and more hydrophobic in nature, show decreased aqueous solubilities relative to that of the API itself. Even though a decrease in solubility is normally not desired within the pharmaceutical industry, a decreased solubility is preferred in some applications of specialty chemicals.

Although it is obvious that not every cocrystal will deliver an improvement in physicochemical properties relative to that of the active ingredient, we have shown that systematic changes to the molecular nature of the cocrystallizing agent combined with control over the way that the individual building blocks are organized within the crystalline lattice makes it possible to establish predictable links between molecular structure and macroscopic physical properties. In this context, cocrystals may therefore offer unique opportunities for developing new solid forms in which a variety of desired physical properties can be tuned in a predictable manner.

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Supporting Information Available: Detailed procedures for synthesis and solubility studies along with crystallographic data for **A1**−**A5** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Kerns, E. H.; Di, L. *Drug-like Properties: Concepts, Structure Design and Methods: from ADME to Toxicity Optimization*; Elsevier: Amsterdam, 2008, pp 7−9. (b) Basavoju, S.; Boström, D.; Velaga, S. P. *Pharm. Res.* **2008**, *25*, 530.
(2) Lipper, R. B. *Mod. Drug Discovery* **1999**, *2*, 55.
(3) (a) *Pharmaceutical Industry Profile 2006*; PhRMA: Washington, DC, 2006. (b) *Mass Spectrometry in Drug Metabolism and Pharmacokinetics*; Ramanathan, R., Ed.; Wiley: Hoboken, NJ, 2009; pp 1−4.
(4) Blagden, N.; de Matas, M.; Gavan, P. T.; York, P. *Adv. Drug Delivery Rev.* **2007**, *59*, 617.
(5) Chaumeil, J. C. *Exp. Clin. Pharmacol.* **1998**, *20*, 211.
(6) Agharkar, S.; Lindenbaum, S.; Higuchi, T. *J. Pharm. Sci.* **1976**, *65*, 747.
(7) Aim, K.; Dannenfelser, R.-M.; Zielinski, J.; Wang, B. *J. Pharm. Sci.* **2004**, *93*, 2244.
(8) Torchillin, V. P. *Pharm. Res.* **2007**, *24*, 1.
(9) Rajewski, R. A.; Stella, V. J. *J. Pharm. Sci.* **1996**, *85*, 1142.
(10) Humberstone, A. J.; Charman, W. N. *Adv. Drug Delivery Rev.* **1997**, *25*, 103.
(11) (a) Goldberg, I. *CrystEngComm* **2008**, *10*, 637. (b) Aakeröy, C. B.; Salmon, D. J. *CrystEngComm* **2005**, *7*, 439. (c) Banerjee, R.; Saha, B. K.; Desiraju, G. *CrystEngComm* **2006**, *8*, 680. (d) Saha, B. K.; Nangia, A.; Jaskólski, M. *CrystEngComm* **2005**, *7*, 355. (e) Aakeröy, C. B. *Acta Crystallogr.* **1997**, *B53*, 569. (f) Braga, D.; Brammer, L.; Champness, N. R. *CrystEngComm* **2005**, *7*, 1. (g) Aakeröy, C. B.; Desper, J.; Fasulo, M.; Hussain, I.; Levin, B.; Schultheiss, N. *CrystEngComm* **2008**, *10*, 1816.
(12) (a) Childs, S. L.; Chyall, L. J.; Dunlap, J. T.; Smolenskaya, V. N.; Stahly, B. C.; Stahly, P. G. *J. Am. Chem. Soc.* **2004**, *126*, 11335. (b) Jayasankar, A.; Reddy, S. L.; Bethune, S. J.; Rodríguez-Hornedo, N. *Cryst. Growth Des.* **2009**, *9*, 889. (c) Trask, A. V.; Motherwell, W. D. S.; Jones, W. *Int. J. Pharm.* **2006**, *320*, 114.
(13) (a) Thalladi, V. R.; Nüsse, M.; Boese, R. *J. Am. Chem. Soc.* **2000**, *122*, 9227. (b) Vishweshwar, P.; Nangia, A.; Lynch, V. M. *Cryst. Growth Des.* **2003**, *3*, 783. (c) Morrison, J. D.; Robertson, J. M. *J. Chem. Soc.* **1949**, *2*, 980. (d) Verweel, H. J.; MacGillavry, C. H. *Nature* **1938**, *142*, 161.
(14) (a) Andreeff, M.; Stone, R.; Michaeli, J.; Young, C. W.; Tong, W. P.; Sogoloff, H.; Ervin, T.; Kufe, D.; Rifkind, R. A.; Marks, P. A. *Blood* **1992**, *80*, 2604. (b) Callery, S. P.; Egorin, M. J.; Geelhaar, L. A.; Nayar, B. S. *Cancer Res.* **1986**, *46*, 4900. (c) Siegel, D. S.; Zhang, X.; Feinman, R.; Teitz, T.; Zelenetz, A.; Richon, V. M.; Rifkind, R. A.; Marks, P. A.; Michaeli, J. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 162.
(15) (a) Shan, N.; Zaworotko, M. J. *Drug Discovery Today* **2008**, *11*, 440. (b) Aakeröy, C. B.; Beatty, A. M.; Helfrich, B. A.; Nieuwenhuyzen, M. *Cryst. Growth Des.* **2003**, *3*, 159. (c) Aakeröy, C. B.; Desper, J.; Helfrich, B. A. *CrystEngComm* **2004**, *6*, 19. (d) Aakeröy, C. B.; Desper, J.; Urbina, J. F. *Cryst. Growth Des.* **2005**, *5*, 1283.
(16) Lauher, J. W.; Fowler, F. W.; Goroff, N. S. *Acc. Chem. Res.* **2008**, *41*, 1215.

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