WHITEPAPER

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Cocrystals: A Regulatory Rebirth

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What is the impact of recent changes in FDA guidance on regulatory and intellectual property issues?

The FDA reclassification of cocrystals as active pharmaceutical ingredients (APIs) has created exciting opportunities for the pharmaceutical industry. That reclassification means cocrystals can now be developed as if they were polymorphs, providing new avenues for dealing with poor API physical properties and extending intellectual property lifetimes. It is important to understand how the revised guideline impacts API development, regulatory submissions, and intellectual property protection. Those topics are discussed in this whitepaper. Also considered is the importance of identifying whether an API is a salt or a cocrystal, a critical classification from a regulatory point of view. In addition, a list of FDA-approved, marketed cocrystals is presented. Finally, recommendations for cocrystal screening, evaluation, formulation, and production at scale are given.

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Introduction

In August of 2016 the US Food and Drug Administration (FDA or Agency) issued a new, draft guidance on cocrystals.[1] In contrast to their 2013 guidance, which required that cocrystals be regarded as drug product intermediates (DPIs),[2] the Agency now assigns cocrystals a regulatory classification similar to that assigned to polymorphs. Different salt forms of the same active moiety are considered different active pharmaceutical ingredients (APIs), but polymorphs and cocrystals of an API are not.

That change has important, positive consequences related to the use and protection of cocrystals in the pharmaceutical industry, including:

1. Cocrystals may be used to overcome poor physical properties of APIs (bioavailability, solubility, stability, processability).
2. The new cocrystal classification provides consistency among FDA guidances, international guidances, and scientific reality.
3. Drug developers no longer have to characterize a third solid form (in addition to the API and solid drug product) in order to use a cocrystal. Instead, they may use existing regulatory documents to guide establishment of the potency, purity, and other critical attributes (ICH Q6A[3]), as well as the stability (ICH Q1A[4]), of a cocrystal API.
4. Manufacturers may use existing manufacturing facilities and supply chains to produce and distribute cocrystal APIs. Additionally, drug product expiration dates are no longer linked to API or DPI manufacture.
5. New Drug Application (NDA) filers may list cocrystal patents as drug substance patents in the FDA's Orange Book.[5]
6. Abbreviated New Drug Application (ANDA) filers may use a 505(j) application for cocrystals instead of the more time-consuming 505(b)(2) application required for salts.

[1] Food and Drug Administration; Draft Guidance; *Regulatory Classification of Pharmaceutical Co-Crystals, Guidance for Industry*; Rev.1; August, 2016.
[2] Food and Drug Administration; Guidance for Industry, *Regulatory Classification of Pharmaceutical Co-Crystals*; April, 2013.
[3] ICH Harmonised Tripartite Guideline Q6A; *Specifications: Test Procedures And Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*; October 6, 1999.
[4] ICH Harmonised Tripartite Guideline Q1AR(2); *Stability Testing of New Drug Substances and Products*; February 6, 2003.
[5] Food and Drug Administration; *Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)*; 36th Ed.; 2016.

What are cocrystals?

The FDA has defined cocrystals as "Crystalline materials composed of two or more molecules within the same crystal lattice."[1] It was pointed out that such a definition, while understandable from a regulatory classification perspective, has some deficiencies from a scientific perspective.[6] An easy way to think of cocrystals is that they are unique crystalline arrangements composed of two or more components, a component being an atom, ionic compound, or molecule.

An example is the fluoxetine hydrochloride benzoic acid cocrystal. Fluoxetine, a molecule discovered by Eli Lilly and Company (Lilly) in 1972 is an exceptionally-active serotonin uptake inhibitor used to treat various mental disorders. The hydrochloride salt of fluoxetine, the API in Lilly's marketed drug Prozac®, exists as a single-component crystal.[7] But it also forms cocrystals with some small carboxylic acids, including one composed of equimolar amounts of fluoxetine hydrochloride and benzoic acid (Figure 1).[8] In that cocrystal one component is a salt and the second component is a molecule.[9] Cocrystals have been found where the components are molecules, organic salts, inorganic salts, and mixtures thereof.[10]

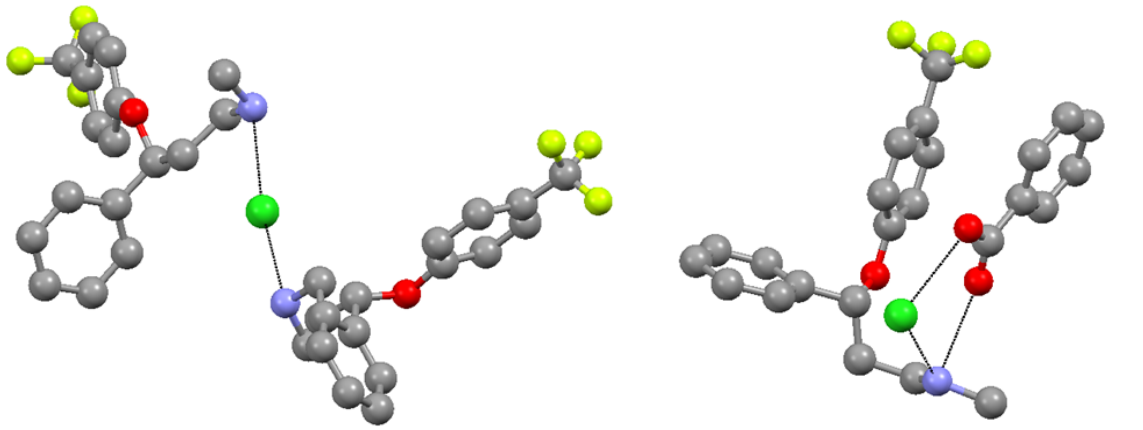


Figure 1. The structures of fluoxetine hydrochloride and the fluoxetine hydrochloride benzoic acid cocrystal.

[6] Aitipamula, S. *et al Cryst. Growth Des.* **2012**, *12*, 2147-2152.
[7] Robertson, D. W. *et al J. Med. Chem.* **1988**, *31*, 185-189.
[8] Childs, S. L. *et al J. Am. Chem. Soc.* **2004**, *126*, 13335-13342.
[9] The new FDA draft guidance classifies products that contain both cocrystal and salt components as salts; see footnote 1.
[10] Stahly, G. P. *Cryst. Growth Des.* **2009**, *9*, 4212-4229.

How can I tell a salt from a cocrystal?

The new FDA guidance discusses the crystallization of *two components containing ionizable groups*.[1] When an acidic and basic compound cocrystallize the question arises, is the crystal a salt or cocrystal? If the acidic proton is fully transferred to the base it is a salt, if not, it is a cocrystal. Specifically, a criterion based on pK_a difference (<1) was proposed by the Agency. They did however, recognize that not all situations are clear cut and stated that "If however, you believe that the classification of the pharmaceutical solid as a salt or co-crystal is not predicated on these relative pKa values, use spectroscopic tools and other orthogonal approaches to provide evidence to the contrary."

From a scientific standpoint, prediction of salt formation based on a ΔpK_a criterion should be approached with caution. While regulators need to classify structures, in reality there are not always clear distinctions that can be made. Such is the case of salts and cocrystals. First, it must be remembered that the pK_a values used in predicting acid-base behavior are those measured in water. In other solvents or in a solventless crystal the values can be quite different. Benzoic acid, which has a reported pK_a of about 4, has a pK_a of about 11 in DMSO!

Secondly, when the ΔpK_a between a cocrystallized acid-base pair is small, whether the acidic proton is retained by the acid, transferred to the base, or shared, depends on the crystal environment. Crystals containing an acid and a base have been found that exist in two polymorphic forms, one of which is a salt and the other of which is a cocrystal (Figure 2).[11] The phenomenon of proton transfer in crystals (the salt-cocrystal continuum) and the factors affecting it have been discussed in the literature.[12] Analytical techniques useful in distinguishing cocrystals from salts are discussed below in the section titled *What techniques can be used to differentiate a salt from a cocrystal?.*

[11] Frampton, C. Salt-Cocrystal interface studies: The importance of being Hydrogen. *Scientific Update 3rd Winter Process Chemistry Conference*, Bath, UK, Dec. 14-16, 2015.
[12] Childs, S. L. *et al Mol. Pharmaceutics* **2007**, *4*, 323-338.

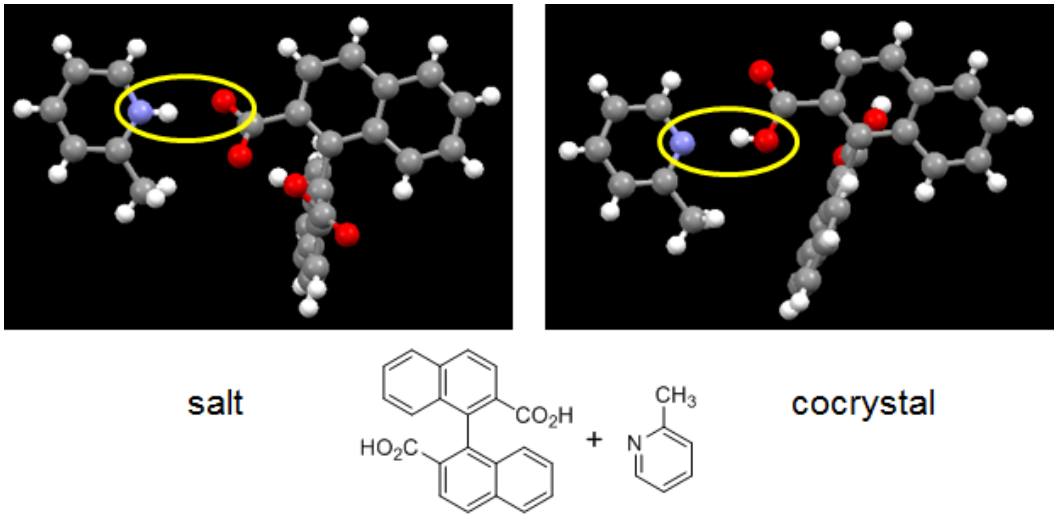


Figure 2. An example of polymorphs of a two-component crystal, one a salt and one a cocrystal.

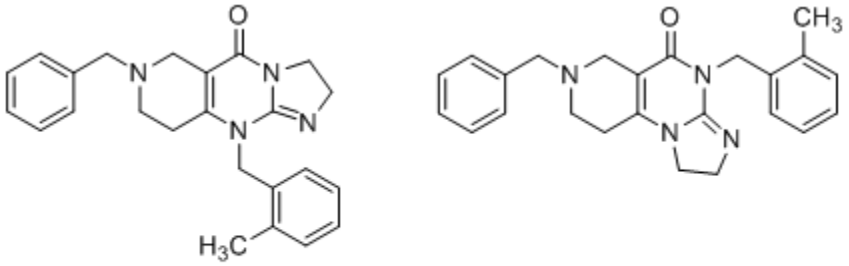
Is it important to know if an API is a salt or a cocrystal?

There are two reasons why it is important to know specifically if an API is a salt or a cocrystal. From a regulatory perspective, a different salt of a drug is considered a different API[13] whereas a new cocrystal is not.[1] That means that seeking approval of a drug product containing a salt of an approved API requires an ANDA 505(b)(2) application, which requires Agency review of clinical data to assess safety and effectiveness. Note, however, that a 505(b)(2) application can rely on clinical data found in the literature or generated by the original NDA filer. On the other hand, to seek approval of a drug product containing a cocrystal of an approved API only an ANDA 505(j) application need be used. That application does not require FDA review of clinical data.

A second reason to understand if an API is a salt or cocrystal is related to intellectual property (IP) protection. Patents are frequently issued that cover salts and cocrystals of APIs. What would happen if you were to obtain a patent on a cocrystal that was later shown to be a salt (or vice versa)? Would the validity of your claim to that cocrystal (or salt) be upheld in litigation? Such a situation is reminiscent of the one that led to the legal quagmire surrounding TIC10. [14] In that case, a patent issued claiming the wrong, inactive isomer of an API that was being clinically evaluated by the patent licensee. Those who discovered the mistake filed a patent application claiming the correct, bioactive isomer

[13] Bioavailability and Bioequivalence Requirements *Code of Federal Regulations* 21 CFR 320.1(c).
[14] Borman, S. *Chem. Eng. News* **2014**, *92* (23), 32.

(Figure 3). Since there are now two claims to the same anticancer drug, both the patent and the patent application are at risk.[15] The outcome remains to be decided.



linear structure
inactive

angular structure
active

Figure 3. TIC10 isomers.

What techniques can be used to differentiate a salt from a cocrystal?

As mentioned by the FDA, there are "spectroscopic tools and other orthogonal approaches"[1] available to determine the extent of proton transfer. An approach often considered is single-crystal X-ray structure determination. The results from such studies must be viewed with caution, however, because protons are notoriously difficult to locate using X-ray data. It is common to simply normalize proton positions by placing them at average, neutron-diffraction-determined distances from the atoms to which they are bonded and not refine them further.[16] In such cases proton locations are approximate only and therefore unusable to distinguish a salt from a cocrystal.

Even if X-ray data are good enough to locate protons from electron difference maps, it must be remembered that X-rays are diffracted by electrons. The proton's single electron in a covalent X–H bond is displaced toward the more electronegative X atom so that the centers of gravity of the nucleus (proton) and electron of the hydrogen atom are no longer coincident. So what should be taken as a proton position from an electron density map? The center of gravity of the electron cloud?

A technique that locates nuclei as opposed to electrons, neutron diffraction, is particularly useful in this situation. Neutron diffraction data are more precise than X-ray diffraction data by an order of magnitude.[17] In a neutron diffraction experiment the centers of gravity of nuclei are located, allowing location of protons as accurately as other nuclei. However,

[15] The patent claims incorrect chemical structure, making the claim potentially unenforceable. The patent application claims the same anticancer drug, making the claim potentially invalid for being obvious over the prior art, albeit with corrected chemical structure.
[16] Steiner, T. *Angew. Chem. Int. Ed.* **2002**, *41*, 48-76.
[17] Jeffrey, G. A.; Lewis, L. *Carbohydr. Res.* **1978**, *60*, 179-182.

neutron sources are few and relatively large crystals are required for single-crystal work, making the technique available only with difficulty.

Vibrational spectroscopy can sometimes be used to differentiate a salt from a cocrystal. If one component is a carboxylic acid, carbonyl stretching vibrations in the infrared (IR) spectrum are indicative. The carbonyl groups of carboxylic acids exhibit strong stretching vibrations between 1660 and 1740 cm^{-1} in the IR spectrum.[18] On saltification, the CO_2^- anion exhibits an anti-symmetric stretching vibration between 1540 and 1650 cm^{-1} and a symmetric vibration between 1360 and 1450 cm^{-1}.[19] Other types of IR data may also be useful. For crystalline solids having O–H···O hydrogen bond interactions, the frequency of the O–H stretching vibration in their IR spectra has been correlated with the O–O distance.[20]

Solid-state nuclear magnetic resonance (ssNMR) spectroscopy is another technique that can be used to differentiate a salt from a cocrystal. Natural-abundance, ^{15}N ssNMR was used, along with single-crystal X-ray diffraction studies, to study the structures of cocrystals/salts of an ErbB2 inhibitor with three dicarboxylic acids.[21] Using cross polarization, magic angle spinning (CPMAS) data collection conditions and short contact times, nitrogen atoms bearing protons were identified. It was found that the chemical shift positions of peaks arising from unprotonated nitrogens varied somewhat compound-to-compound because of differences in hydrogen bonding, but protonation of those nitrogens resulted in much larger chemical shift differences. For example, a particular nitrogen atom resonates at –118 ppm in the free base (unprotonated), –149 ppm in a succinic acid cocrystal (unprotonated), and –203 and –209 ppm in the malonic acid and maleic acid salts (protonated), respectively. The upfield movement of the nitrogen atom signal by about 50–80 ppm on protonation provides clear and definitive evidence of salt formation.

X-ray photoelectron spectroscopy (XPS) has been used to differentiate salts from cocrystals. In that technique, irradiation of a sample by X-rays causes emission of electrons from the sample surface, their energies being related to the oxidation states of the atoms from which they originated. It was found that the N 1s XPS spectrum of a theophylline:oxalic acid cocrystal was the same as that of theophylline itself.[22] In the XPS spectrum of a theophylline salicylic-5-sulfonate salt the peak from the protonated nitrogen atom is shifted by about 2.3 eV to higher binding energy, indicating the existence of a positive charge on that atom and confirming the formation of a salt.

[18] Lin-Vien, D.; Colthup, N. B.; Fateley, W. G.; Grasselli, J. G. *The Handbook of Infrared and Raman Characteristic Frequencies of Organic Molecules*; Academic Press: San Diego; 1991; p 139.
[19] *Ibid* p 141.
[20] Novak, A. Hydrogen Bonding in Solids: Correlation of Spectroscopic and Crystallographic Data. In *Large Molecules*; Vol. 18; Springer Berlin Heidelberg: Berlin, Heidelberg, 1974, pp 177-216.
[21] Li, Z. J.; Abramov, Y.; Bordner, J.; Leonard, J.; Medek, A.; Trask, A. V. *J. Am. Chem. Soc.* **2006**, *128*, 8199-8210.
[22] Stevens, J. S.; Byard, S. J.; Schroeder, S. L. M. *J. Pharm. Sci.* **2010**, *99*, 4453-4457.

Why are cocrystals useful?

One part of the drug development process entails selection of the 'best' solid form (crystalline or non-crystalline) of the API. "Best' in this instance is a form having a set of physical properties that allow it to be consistently manufactured and processed into efficacious drug product. For crystalline APIs, those properties include melting point, solubility, dissolution rate, hygroscopicity, habit, and chemical and physical stability.

Traditionally the approach used to overcome poor physical properties of a solid API involves looking for different polymorphic forms or, if the API is ionizable, looking for crystalline salts. When searching for salts, standard practice is to use only counter-ions that have been used in regulatory-approved APIs. The reason for that is to avoid the risk of an API failing toxicity or other tests because of the counter-ion. On the other hand, pharmaceutically-acceptable cocrystals can be prepared from a much larger pool of co-formers. Compounds that are not salt potential counter-ion sources, such as sugars and amino acids, can be used. In addition, salts of standard salt counter-ions and other pharmaceutically-acceptable, ionizable compounds are good potential co-formers.

Since a cocrystal is a *unique* material, its properties will differ from the properties of the individual, crystalline components. Cocrystals containing an API and a second, non-bioactive component have been found that eliminate hygroscopicity,[23] tune melting points,[24] increase dissolution rate,[8,25] and, when properly formulated, enhance bioavailability.[26]

Since an increasing number of organic drug molecules developed are BCS[27] class II or IV, a common property targeted for improvement by cocrystals is poor aqueous solubility. There are many examples of cocrystals having higher dissolution rates compared to the APIs themselves. In those situations cocrystals are like amorphous materials in that they provide a supersaturated concentration of an API in the body for a long enough time for absorption to occur (a supersaturating drug delivery system).[28] It must be realized that a cocrystal typically does not affect the *equilibrium* solubility of an API. That is because cocrystals usually dissociate in solution because they are held together by relatively weak chemical bonds.

Another advantage offered by cocrystals is intellectual property. Since the formation of cocrystals is currently unpredictable, those that are discovered and found to have advantageous properties can be patented. In addition, now that cocrystals are considered

[23] Trask, A. V. *et al Cryst. Growth Des.* **2005**, *5*, 1013-1021.
[24] Fleischman, S. G. *et al Cryst. Growth Des.* **2003**, *3*, 909-919.
[25] Remenar, J. F. *et al J. Am. Chem. Soc.* **2003**, *125*, 8456-8457.
[26] Childs, S. L. *et al Mol. Pharmaceutics* **2013**, *10*, 3112-3127.
[27] The Biopharmaceutics Classifications System (BCS) is a system to classify drugs on the basis of their solubility and permeability. Class II drug substances exhibit low solubility and high permeability whereas Class IV exhibit low solubility and low permeability. Amidon GL. *et al Pharm Res* **1995**, *12*, 413-420.
[28] Brouwers, J. *et al J. Pharm. Sci.* **2009**, *98*, 2549-2572.

to be APIs, patents claiming them can be listed as drug substance patents in the FDA's Orange Book.[29]

Are there any approved drug products that contain cocrystals?

Yes. It is interesting that cocrystals were tested as pharmaceuticals in the late 19th century. An 1895 pharmaceutical text, Modern Materia Medica (4th edition) describes several cocrystals.[10] One of those was hypnal, a cocrystal containing the analgesic antipyrine and the sedative chloral, which was reported to alleviate pain and produce quiet sleep when given to patients with troublesome coughs.

Probably the first commercial drug product in the U.S. that contained a cocrystal was Mead Johnson's Beta-Chlor.[30] That cocrystal, composed of chloral hydrate and betaine, was patented in 1962. Chloral hydrate, which had been on the market since its sedative properties were discovered around 1869, was classified as an unapproved drug on passage of the Federal Food, Drug, and Cosmetic Act of 1938. It remains so classified to date but is now a schedule IV controlled substance. The upshot is that the first cocrystal-containing drug product sold in the U.S. did not go through an approval process.

Depakote® was approved in the U.S in 1983 for treatment of epilepsy and in 1996 for the prevention of migraine headaches. The API is a cocrystal of valproic acid and sodium valproate, a common type of cocrystal found for carboxylic acids. The Depakote package insert refers to the API as a "stable co-ordination compound".

Suglat® tablets, which contain the active ingredient ipragliflozin as a cocrystal with L-proline, were approved for use against type 2 diabetes in Japan in 2014.

Entresto® was approved in the U.S. in 2015 to treat heart failure. The active ingredient, termed a "co-crystal" by the European Medicines Agency but a "complex" by the FDA, contains two bio-active molecules, sacubitril and valsartan. It is interesting that the cocrystal is a hemi-pentahydrate of the sodium salt of sacubitril and the di-sodium salt of valsartan (Figure 4). Entresto® is an example of what have been called multi-drug cocrystals.[31]

[29] Food and Drug Administration; *Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)*; 36th Ed.; 2016.
[30] O'Nolan, D. *et al Cryst. Growth Des.* **2016**, *16*, 2211-2217.
[31] Thipparaboina, R. *et al Drug Discovery Today* **2016**, *21*, 481-490.

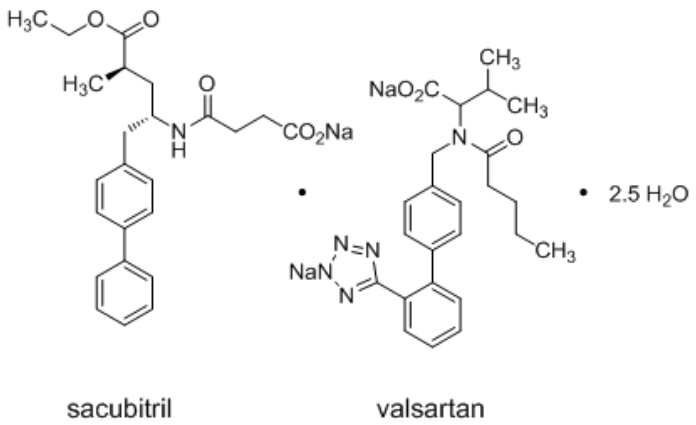


Figure 4. The components of the cocrystal in Entresto®.

What is the most successful way to develop cocrystals?

Development of a successful cocrystal involves several technical challenges. Finding cocrystals is currently an empirical exercise comprising selection of pharmaceutically-acceptable coformers and utilization of appropriate reaction conditions to favor their formation.

Triclinic Labs' scientists have carried out hundreds of cocrystal screens. We utilize coformers that are salt counter-ions in approved drug products, as well as simple salts of those (acetic acid and sodium acetate, for example). Other coformers are selected from food substances or materials on the FDA's Everything Added to Food in the U. S. (EAFUS) or Generally Recognized as Safe (GRAS) lists. However, not all the compounds on the EAFUS and GRAS lists can be ingested in large enough quantity or have been sufficiently evaluated toxicologically to be useful coformers. The specifics of each API and intended drug product should be carefully considered during coformer selection.

If the goal of cocrystal screening is to overcome poor aqueous solubility, it is standard practice to utilize water-soluble coformers. However, better coformer solubility does not necessarily mean a cocrystal containing that coformer will have improved dissolution performance. A highly water-soluble coformer can create such a high level of drug concentration that it cannot be maintained for the period of time necessary for absorption to occur. Finding just the right coformer can be a challenge.

Experimentally, cocrystal screening is more complicated than salt screening. Nucleation needs to occur within specific concentration ranges to avoid crystallization of components separately. Where those ranges occur depends on the difference in solubility of the components being tested. Consideration of ternary phase diagrams shows how the likelihood of cocrystal nucleation from a simple solvent evaporation experiment is increased when the components have similar solubilities (Figure 5). Triclinic has amassed a database of coformer solubility data and designs solvent-based cocrystal experiments

based on those data and API solubility data. In addition, we use multiple solventless techniques.

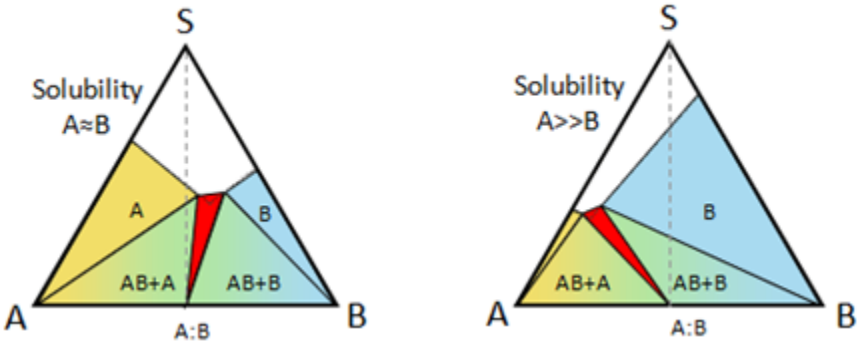
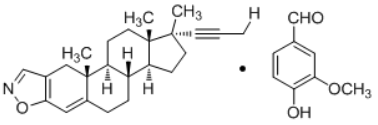


Figure 5. Ternary phase diagrams showing the location of the cocrystal nucleation space (red) when the cocrystal components (A and B) have similar solubilities in solvent S (left) and dissimilar solubilities in solvent S (right).

Once a cocrystal has been found and characterized, its dissolution behavior should be studied. We have seen potentially-useful cocrystals abandoned because of data generated by improperly-designed dissolution measurements. For example, initial dissolution testing should not be carried out under sink conditions since that may not allow measurement of the time during which supersaturation is maintained.

Triclinic carries out cocrystal formulation studies since formulation can be critical to cocrystal performance. That is clearly illustrated by a study of the dissolution behavior and *in-vivo* (rat) bioavailability of danazol and a danazol-vanillin cocrystal.[26] On direct comparison *in vivo* the cocrystal provided about three times the maximum blood level of danazol than did danazol itself (Figure 6). Inclusion of the appropriate excipients (solubilizer and nucleation inhibitor) with the cocrystal increased the maximum blood level to twenty times that found on dosing danazol itself.



API or CC	TPGS (%)	HPC (%)	T_{max} (hr)	C_{max} (ng/mL)	AUC (ng/mL/h)
API	0	0	1.5 ± 0	9.5 ± 4	36 ± 17
API	1	2	1.3 ± 0.3	14 ± 13	46 ± 37
CC	0	0	0.7 ± 0.3	28 ± 5	64 ± 24
CC	1	0	0.42 ± 0.14	85 ± 29	115 ± 33
CC	0	2	1.5 ± 0	51 ± 16	179 ± 59
CC	0.5	2	1.3 ± 0.4	156 ± 14	490 ± 3
CC	1	2	1.2 ± 0.3	190 ± 11	475 ± 42

Figure 6. Results from an *in-vivo* (rat) bioavailability study of formulated and unformulated danazol and danazol-vanillin cocrystal.

Triclinic is also experienced at developing crystallization methods that can be used to produce a crystalline product, including cocrystals, consistently at scale. A thorough understanding of the phase behavior of the crystallization system is important to development of a robust process. Because cocrystals are held together by relatively weak bonds, even washing them with solvent can result in decomposition into their components. However, with the appropriate background information, processes to make cocrystals at large scale are developable.[32]

Is cocrystal technology useful outside of the pharmaceutical industry?

Indeed it is. Some interesting applications of cocrystals include rocket fuel,[33] stabilized explosives,[34] non-linear optical materials,[35] and nutraceuticals.[36]

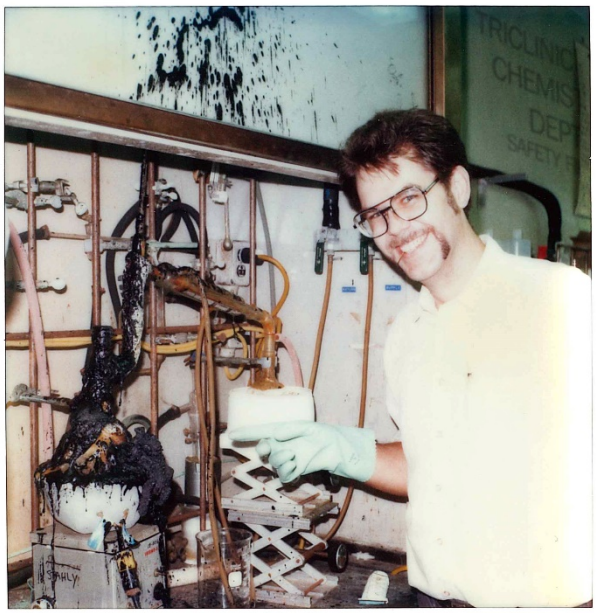
[32] Sheikh, A. Y. *et al CrystEngComm* **2009**, *11*, 501-509.
[33] Levinthal, M. L. U.S. Patent 4,086,110, April 25, 1978.
[34] Bolton, O. *et al Cryst. Growth Des.* **2012**, *12*, 4311-4314.
[35] Etter, M. C. *et al Chem. Mater.* **1989**, *1*, 12-14.
[36] Sekhon, B. S. *DARU J. Pharm. Sci.* **2012**, *2*, 16-25.

Recommendations for cocrystal development

Cocrystals are without a doubt an excellent option for drug development to enhance bioavailability, stability, and processability of APIs. That is true for both ionizable and non-ionizable drugs. The FDA draft guidance[1] opens new opportunities to develop cocrystals as APIs. However, challenges remain, including coformer selection, analytical characterization, and formulation. In addition, preparations of patent applications claiming cocrystals need to be carefully done, not only to result in patent issuance but to provide strong patents that can survive litigation. Triclinic Labs believes that our experience and knowledge of cocrystal research and screening, our analytical expertise, our use of multidisciplinary tools to analyze cocrystals, and our unique experience of serving as experts in numerous patent litigations make us an industry leader in pharmaceutical cocrystal development.

About the Author

Dr. Stahly is Chief Operating Officer of Triclinic Labs. Dr. Stahly has over 30 years of experience in the specialty and pharmaceutical chemical industries. Since obtaining a Ph.D. in Organic Chemistry from the University of Maryland, he held positions of increasing responsibility at the Ethyl (now Albemarle) Corporation, was Chief Operating Officer and Chief Scientific Officer of SSCI, Inc., and was Vice President of Scientific Operations of Aptuit. His expertise includes process organic chemistry, crystallization, solids analysis, X-ray diffraction, pharmaceutical preformulation, and chiral chemistry.
He is an inventor of 44 US patents and author of 33 publications, including peer-reviewed papers and book chapters. In addition, Dr. Stahly has lectured extensively throughout the world and has taught numerous courses on solid-state chemistry.



Dr. Stahly completes his first successful tert-Butyl Ester decomposition reaction.

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