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Polymorphs, Salts, and Cocrystals: What's in a Name?

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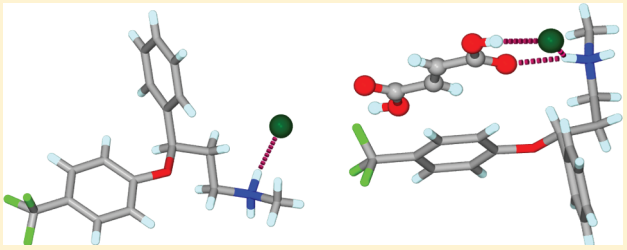
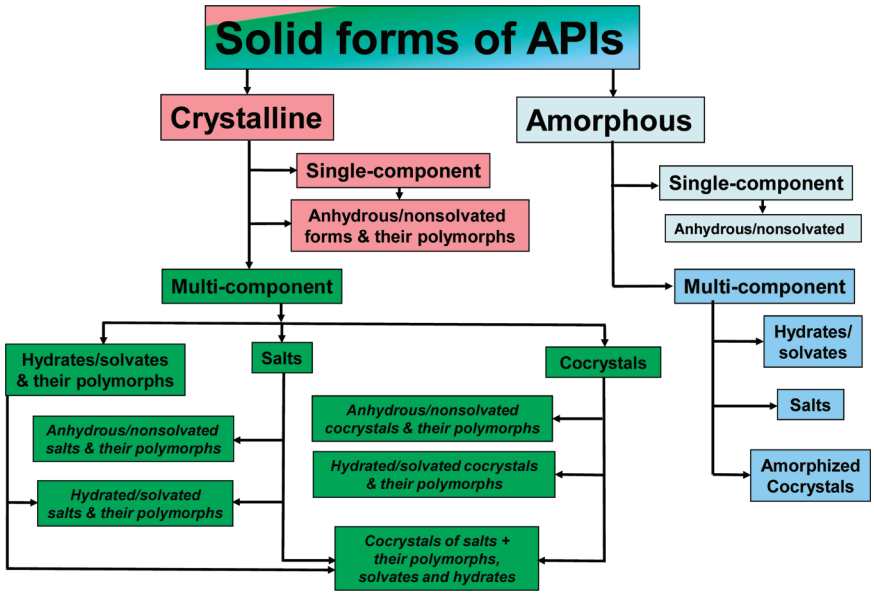
ABSTRACT: The December 2011 release of a draft United States Food and Drug Administration (FDA) guidance concerning regulatory classification of pharmaceutical cocrystals of active pharmaceutical ingredients (APIs) addressed two matters of topical interest to the crystal engineering and pharmaceutical science communities: (1) a proposed definition of cocrystals; (2) a proposed classification of pharmaceutical cocrystals as dissociable "API-excipient" molecular complexes. The Indo−U.S. Bilateral Meeting sponsored by the Indo−U.S. Science and Technology Forum titled *The Evolving Role of Solid State Chemistry in Pharmaceutical Science* was held in Manesar near Delhi, India, from February 2−4, 2012. A session of the meeting was devoted to discussion of the FDA guidance draft. The debate generated strong consensus on the need to define cocrystals more broadly and to classify them like salts. It was also concluded that the diversity of API crystal forms makes it difficult to classify solid forms into three categories that are mutually exclusive. This perspective summarizes the discussion in the Indo−U.S. Bilateral Meeting and includes contributions from researchers who were not participants in the meeting.



An important aspect of drug development is determining which specific solid form of an active pharmaceutical ingredient (API) should be selected for scale-up, formulation activities, and clinical trials. This process is a nontrivial exercise since an API can be polymorphic,[1] meaning that it can exist in two or more crystal forms. Frequently, the crystal forms of an API exhibit low solubility, and it might be appropriate to use a more soluble amorphous form[2] or a more soluble multi-component form,[3] such as a salt form — for ionizable APIs — or a cocrystal form[4] for neutral APIs. Furthermore, APIs are typically amenable to formation of multiple component crystals such as solvates and hydrates. In short, as presented in Scheme 1, for most APIs, there are numerous possible solid forms that can be obtained and subsequently must be investigated and characterized as part of drug development. Each solid form of an API has distinct physicochemical properties, and finding the optimal solid form is important to intellectual property, processing, enabling drug delivery and is a key to obtaining regulatory approval. Therefore, although the search for new solid forms increases the costs and time associated with pharmaceutical development, there are also opportunities for making better medicines. These opportunities have spawned the development of new technologies for solid form discovery such as high-throughput screening[5] and the formation of companies to conduct solid form screening.

Pharmaceutical cocrystals represent a subset of cocrystals, a long known[6] but little-studied class of compounds. Pharmaceutical cocrystals have quickly evolved from relative obscurity to a widely studied class of crystal forms in the context of pharmaceutical science and engineering. Their attraction to pharmaceutical scientists is that they significantly diversify the number of crystal forms that exist for APIs and they can afford improvements in physicochemical properties[7] of clinical relevance. It is noteworthy that APIs, that is, molecules or ions with hydrogen bond donor or acceptor moieties, mean that all APIs, including nonionizable APIs, can be made as cocrystals using a rational approach that involves supramolecular synthons.[4] In addition, APIs that contain aromatic rings are amenable to formation of cocrystals sustained by stacking or charge transfer interactions,[8] and ionic cocrystals[9]

Scheme 1. The Diversity of Solid Forms That Can Exist for an API Is Extensive and Has Been Exacerbated by the Evolution of Multi-Component Solid Forms of APIs Such As Stoichiometric Cocrystals[a]



[a]Note that non-stoichiometric forms such as amorphous polymer dispersions and inclusion compounds are not included in the above chart.

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involving inorganic salts have recently emerged. Improved medicines are therefore likely to be a common result of applying the technology of pharmaceutical cocrystallization. That there is heightened awareness of pharmaceutical cocrystals is evidenced by the number of meetings that have been devoted to the subject in the past several years, patent activity, and special issues of *Molecular Pharmaceutics* (quickly followed by a feature article in the June 18, 2007 issue of *Chemical & Engineering News*) and *Crystal Growth & Design*. Most recently, the need to address and classify pharmaceutical cocrystals from a regulatory perspective has been recognized by the United States Food and Drug Administration (FDA), which released a draft guidance on the subject of regulatory classification of pharmaceutical cocrystals[10] in December 2011.

This draft guidance was rather timely in the context of the Indo-U.S. Bilateral Meeting on the *Evolving Role of Solid State Chemistry in Pharmaceutical Science* that was held in the Heritage Village Resort & Spa located in Manesar near Delhi, India, from February 2−4, 2012. The meeting was organized by IISc Bangalore and IIT Delhi with major funding from the Indo−U.S. Science and Technology Forum. The meeting brought together over 70 industrial and academic researchers from the US and India. The scientific program covered a broad range of subjects and there was a good balance of industrial and academic presentations. The program included presentations by several of the leading academic and industrial groups in cocrystal research, and the final session of Day 2 was devoted to a panel discussion that addressed the recently released draft guidance. Two primary matters raised by the draft guidance were of particular interest to the panel and the audience: (1) the FDA's proposed definition of cocrystals; (2) the FDA's proposal to classify cocrystals as dissociable "API-excipient" molecular complexes. The 90-min session and follow-up email communications were vibrant and interactive with considerable interest and opinion expressed on both matters. This perspective is a summary of these discussions and it highlights the significance of nomenclature and the pressing need to define cocrystals in the context of pharmaceutical science.

DEFINITION OF COCRYSTALS

The following definition of cocrystals was proposed by the FDA in the draft guidance: *Solids that are crystalline materials composed of two or more molecules in the same crystal lattice.* Whereas there is not yet a uniformly accepted definition of cocrystals according to the scientific literature,[4,11] the FDA proposed definition would be much more restrictive than any of the definitions currently used by the scientific community and typically found in the patent literature since it limits cocrystals to molecular components. Furthermore, this definition could be viewed as being ambiguous since every molecular crystal must by definition have two or more molecules in its crystal lattice in order to exhibit the repeating arrangements of molecules that define a crystal. Nevertheless, the proposed definition is in the context of the regulatory perspective on nomenclature of crystal forms of APIs, which presently has two classifications:

FDA Classification of Polymorphs. *Different crystalline forms of the same substance. This may include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms.* Per the current regulatory scheme, different polymorphic forms are considered the same active ingredients.[12]

FDA Classification of Salts. *Any of numerous compounds that result from replacement of part or all of the acid hydrogen of an acid by a metal or a radical acting like a metal; an ionic or electrovalent crystalline solid.* Per the current regulatory scheme, different salt forms of the same active moiety are considered different active ingredients.

The new definition of cocrystals proposed by the FDA would therefore add a third classification that is mutually exclusive from the other two classifications, a situation that is convenient and does not require modification of guidelines associated with polymorphs and salts. However, there is strong consensus among this group of authors that these classifications cannot be mutually exclusive given the practical reality that these three classifications overlap and ignore the scientific and patent literature. For example, one of the seminal papers on pharmaceutical cocrystals addressed the solubility effect caused by cocrystallization of fluoxetine hydrochloride,[13] Prozac, with carboxylic acid cocrystal formers (Figure 1). Whereas Prozac is clearly a salt, how would one classify the carboxylic acid cocrystals under the new FDA's definitions? In a similar vein, Kastelic et al. reported three multicomponent crystalline forms of the antifungal drug fluconazole with three dibasic acids (maleic acid, fumaric acid, and glutaric acid).[14] It is noteworthy that the multicomponent form with maleic acid contains both neutral and ionized maleic acid with one molecule of the ionized fluconazole in the asymmetric unit. Under which of the proposed classifications would such crystal forms be most suited? On the other hand, lithium salts are widely used as APIs and amino acid cocrystals of lithium salts were recently reported.[9b] Would these compounds be defined as cocrystals, salts, or cocrystals of salts? The latter is the most logical choice from a scientific perspective but it then belongs to two classifications. Other contradictions might occur for solvates or hydrates of cocrystals and hemisalts. For example, escitalopram oxalate,[15] a marketed drug, exists in a crystal form that is composed of protonated escitalopram cations, water molecules, oxalate dianions, and diprotonated oxalic acid molecules in the same crystal (Figure 2). How does one classify a hydrated cocrystal of a salt under the new guidelines? One must also consider the full range of cocrystal formers that are likely to be readily accessible, useful, and have already been scientifically validated. Inorganic salts (i.e., "ionic cocrystals", a term that has only been introduced very recently),[9] nonvolatile solvents such as diols and other APIs (combination drugs) might all be appropriate cocrystal formers to include in a library for a screening study. However, this raises yet another question — when does one consider a solvent as being volatile or nonvolatile. Presumably, the matter would be addressed by determining the thermal stability of a particular solid form rather than through general classification. We therefore propose a definition of cocrystal that is much broader than that proposed by the FDA but is consistent with the scientific literature: *cocrystals are solids that are crystalline single phase materials composed of*

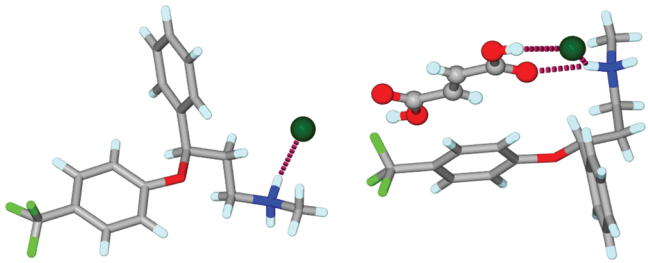

Figure 1. Fluoxetine HCl, the active ingredient of Prozac, (left) and its cocrystals (right) with carboxylic acids illustrate the dilemma one faces with the proposed FDA definition of cocrystals since carboxylic acid cocrystals might be classified as being a cocrystal of a salt.

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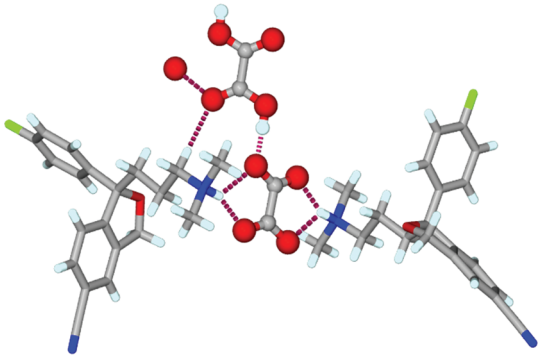


Figure 2. The crystal structure of escitalopram oxalate, a marketed drug, reveals the presence of protonated escitalopram cations that hydrogen bond to oxalate dianions, water molecules, and oxalic acid molecules in the same crystal.

two or more different molecular and/or ionic compounds generally in a stoichiometric ratio. Notably this definition excludes inclusion compounds of the type cited as examples by the FDA in their draft guidance, for example, cyclodextrin complexes and polymer dispersions. This definition also excludes solid solutions that typically occur when two compounds that are nearly identical in molecular geometry and isostructural are crystallized together. Complexes, dispersions, and solid solutions might also be regarded as multicomponent APIs in a formulated drug product but they are not encompassed by the definition we propose. The proposed definition would not exclude solvates or hydrates, which are conceptually related to cocrystals from a supramolecular perspective.[16] Alternatively, should it be deemed appropriate to keep solvates and hydrates separately classified from cocrystals? If so, the above definition might be modified as follows: *cocrystals are solids that are crystalline single phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts.* Compounds that would be regarded as "hemi-salts" will thereby be encompassed by this definition.

CLASSIFICATION OF COCRYSTALS

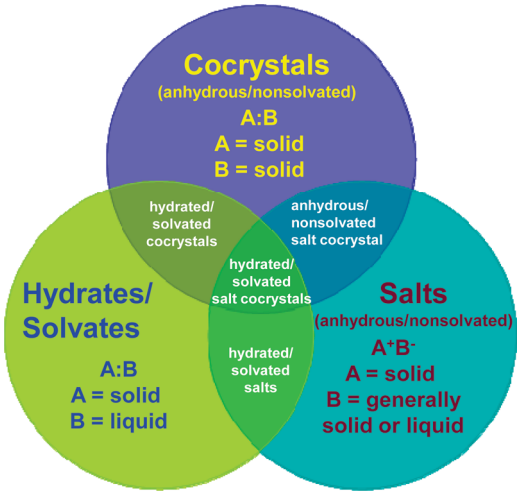
The following classification has been proposed by the FDA: *Cocrystals should be classified within the Agency's current regulatory framework as dissociable "API-excipient" molecular complexes. They may then be treated as a "drug product intermediate" rather than as a drug.*

Should this classification be adopted, then there are several implications:

1. Cocrystal containing drug products will not be considered to contain new APIs.
2. New drug applications, NDAs, and abbreviated NDAs, ANDAs, claiming to contain a cocrystal form will have to prove the extent of proton transfer.
3. The cocrystal must be shown to dissociate in vivo prior to reaching its active site. The nature and location of the putative active site varies greatly between different drug classes, such that there is significant ambiguity about how to address the dissociation requirement, especially in the case of topically active drugs (applied on skin or orally active within the GI tract, for instance).
4. The API cocrystal which — by definition — is a crystalline multicomponent chemical compound would be considered analogous to the "API-excipient" blend that overwhelmingly represents a physical mixture of an API and excipient(s).

As detailed earlier herein, the nature of multicomponent solid forms is such that there is significant overlap between salts, cocrystals, and hydrates (Scheme 2), and this can create

Scheme 2. Multi-Component Solid Forms Inherently Overlap with One Another and in Addition They Can Exhibit Polymorphism



difficulties when it comes to classification. With this in mind, the strong consensus of the authors is that cocrystals should naturally be grouped with salts for this and a number of other reasons:

- Given that the difference between a salt and a cocrystal might just be the movement of a proton by around 1 Å, is there any reason why the type of interaction in a solid form should in effect be used to classify it? For example, a formic acid solvate of an API could be classified as a solvate, a cocrystal, or a salt. However, only the nature of the interaction between the two components will tell one how to classify such a molecular complex. Does the nature of this interaction have any relevance at all to pharmaceutical science and clinical performance?
- The issue of the "salt cocrystal continuum",[17] which was raised by the FDA, has not been studied in sufficient breadth or depth to conclude the frequency or importance of this phenomenon. Furthermore, it becomes moot if salts and pharmaceutical cocrystals are grouped together.
- Like salts, cocrystals have defined stoichiometries, and similar solution speciation characteristics, such as common-component effects (similar to common ion effects of salts), multiple ionization (API and coformer), and association (self-association and complexation).
- Similar to salts, cocrystals will exhibit a solubility product (K_{sp}) and a pH_{max} (that specifies the thermodynamic stability region of the cocrystal).[18] These properties are of paramount importance in the performance aspects and analytical procedures that cocrystals will require (such as level of coformer, common components) to provide reasonable assurance of their safety and effectiveness.
- There are already marketed drugs that could be classified as cocrystals. Caffeine citrate,[19] Depakote (the valproic acid cocrystal of sodium valproate),[20] and Escitalopram oxalate are marketed as salts but they could be classified as cocrystals according to our proposed definition.

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- Polymorphism in cocrystals (different packing arrangements with the same composition, e.g. carbamazepine: saccharin[21] (Figure 3), piroxicam: 4-hydroxybenzoic acid[11d] and hydrates of cocrystals)[22] defy the idea that cocrystal formers play the same role as that of an excipient. Rather, cocrystals are novel solid forms that can be patented[23] and are known to modulate physicochemical properties such as solubility in either direction.[13] This means that they could be applicable in either immediate release or extended release formulations unlike the "API-excipient complexes".

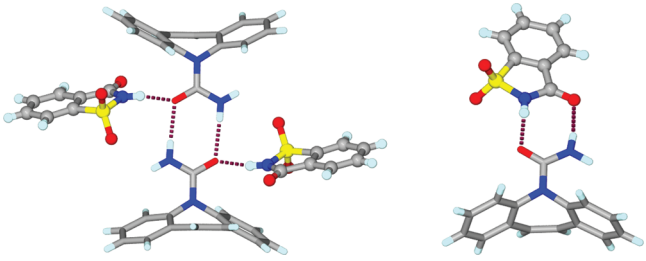

Figure 3. Form I (left) and form II (right) of carbamazepine saccharin illustrate how supramolecular synthons can lead to polymorphism in cocrystals.

- The position of the proton in autoionizable APIs such as Cefdinir (which could exist in zwitterionic or molecular form) and Triclabendazole (polymorph II exists with tautomeric forms in the asymmetric unit)[24] is not considered relevant for classification so why does it matter to the debate about salts vs cocrystals?
- The analogy between cocrystals and "API-excipient complexes" is tenuous for a number of reasons:
  - An excipient is supposed to be chemically inert with regard to the API, unlike a cocrystal former whose function is to participate in intermolecular interactions with an API and become an integral part of the resulting crystal structure.
  - Generally, API-excipient blends do not chemically react from either a covalent or noncovalent perspective. If they did, the integrity of the API would be compromised and such excipients would be eliminated as a result of drug-excipient compatibility studies. Nevertheless, excipients, even in stable formulations, might weakly interact with the surface of API particles. However, they do not become part of the crystal structure as in cocrystals.
  - The formation of a cocrystal of an API fully resembles API salt formation since the intent is to alter the properties of the drug substance via a premeditated chemical interaction between the API and the cocrystal former; therefore, it should not be considered as a formulation process of blending an API with excipient(s) to afford a "drug product intermediate." Ultimately, any cocrystal form of an API, just like any salt of an API, would still require appropriate formulation to afford the final dosage form.
- Cocrystals, like salts, represent solid forms that if novel can be patented and they are known to modulate important physicochemical properties such as solubility, stability, or bioavailability. They can therefore be applicable for use as an API in either immediate release or extended release formulations.

CONCLUSION

To answer the question posed in the title of this perspective, a name means everything when it comes to regulatory classification. We assert herein that the classification of cocrystals in pharmaceutical science should be consistent with current scientific thought. This means that pharmaceutical cocrystals should be broadly defined and that they should be grouped with salts. What is not so clear to the authors is whether there should be one, two, or three classes of pharmaceutical solid, all of which can be crystalline or amorphous:

One class: All solid forms of APIs will be classified together under one umbrella and be required to meet the same requirements in terms of purity, stability, and efficacy.

Two classes: (a) Single-component APIs: polymorphs, solvates, or hydrates. (b) Multicomponent APIs: salts, cocrystals, or any other systems where two or more compounds are present in one phase, generally in a stoichiometric ratio, and their polymorphs, solvates, or hydrates.

Three classes: (a) Single-component APIs and their polymorphs; (b) multicomponent APIs and their polymorphs: salts, cocrystals, cocrystals of salts, binary salts; (c) solvates and hydrates of single-component or multicomponent APIs and their polymorphs.

There is no overwhelming consensus among the authors about which of these classifications is most appropriate, although the majority favor the three class option. This would require reclassification of salts and polymorphs as currently defined and classified by the FDA. We look forward to continued debate on this important and topical matter.

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Notes

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