

Section: LIFE SCIENCE

The Challenge for Engineering Pharmaceutical Crystalline Solids: Scientific and Regulatory Affairs Perspectives for Crystal Structure Design and Prediction

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**Abstract:**

The Breakthrough into solid-state research has become emerging approach for structure determination of Active Pharmaceutical Ingredients (APIs) and excipients that consequently influence their physicochemical properties, biopharmaceutical and pharmacokinetic profiles. The concept of conventional pharmaceutical salts has been extended to multicomponent crystals which diversity in nature of the non-covalent intermolecular interactions determine the crystal packing patterns within the structures, and thus modulate the native properties of APIs. Therefore, the aim of this review is to highlight how accomplishments in crystallographic research on molecular crystal have influenced their classification and how these new solid phases have been recognized by the regulatory bodies. The advantage to explore the pharmaceutical crystalline solids of one API implies the selection of the form with favorable properties for the development of formulations for pharmaceutical dosage forms.

Keywords: Crystal structure, non-covalent intermolecular interactions, multicomponent crystals, structure-property relationship

1 | INTRODUCTION

Significance for research on the pharmaceutical solid forms

The requirements for investigation new phases the solid forms of pharmaceuticals in forms of Active Pharmaceutical Ingrediants (APIs) and functional excipients, as well testing the stability of the existing ones has been impelled by the increasing growth of 5.8% for oral solid dosage forms (OSD) on the market of contract manufacturing sector through the forecast period of 2017-2028, generating the revenue of US\$ 11.2 Bn in 2019 only

for tablets, within immediate release tablets contribute maximum revenue share. (1) Subsequently, U.S. Food and Drug Administration (FDA) Center for drug Evaluation and Research (OCER) ratio in total approved OSD accounted 53%, 50% and 32% in 2018, 2017, and 2016 respectively. The advantageous of the OSD pharmaceuticals in terms of their cost-effectiveness in terms of manufacturing and handling processes, patient compliant, increased physical and chemical stability, immediate released or controlled-release drug biopharmaceutical profiling are directly influenced by the physic-chemical properties of the selected solid forms of APIs and

excipients combined in this drug delivery formulations. Approximately 40 % of all drugs with market approval and 90 % drug-candidates in drug discovery stage exert poor water solubility being categorized under the Biopharmaceutical Classification System (BCS) classes II (low solubility and high permeability) and IV (low solubility and low permeability). (2, 3)

High R&D cost and time consuming for screening drug candidates among molecular structures beyond Lipinski's the rule of five concept (4), that refers to high molecular mass, high lipophilicity and hydrophobicity (5), as well the declining of drug candidates from pipeline, due to poor water solubility, prompt the drug discovery and development across the solid form selection in order by optimizing the physic-chemical properties biopharmaceutical profiling and downstream processing (flowability, particle size reduction, compacting and etc.) (6) of APIs conveniently to shortcut the development of pharmaceutical formulations for solid dosage forms which are highly share the pharmaceuticals market. Pharmaceutical Salts (PSs) accounts approximately 50% of the total approved APIs by the U.S. Food and Drug Administration (FDA) (7), and half of the top 200 prescribed dosage forms in U.S. (8)

Classification of crystalline solids of pharmaceutical relevance: Pharmaceutical Cocrystals vs. Pharmaceutical Salts

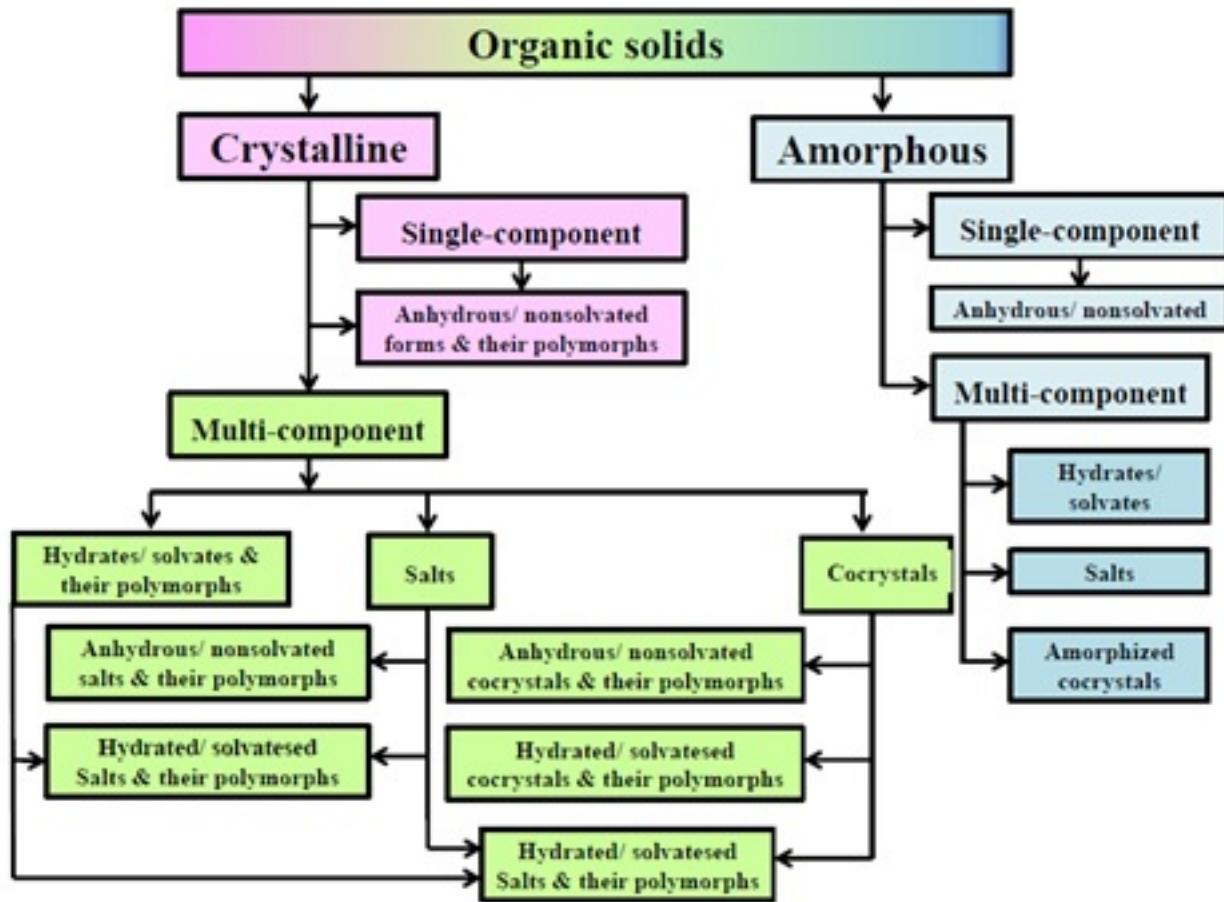
Aside of molecular adducts, inclusion complexes, solid solution and dispersion, multicomponent crystals of pharmaceutical relevance, depicted on the , consider Pharmaceutical Cocrystals (PCCs), Pharmaceutical Salts (PSs) and Solvates formed by cocrystallization of at least two component, one of which API molecule together with neutral conformer, ion or solvent, respectively as a single phases

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with defined stoichiometric ratio of components (9, 10)Figure 1

The advantage of classification the multicomponent crystals come out as a consequence of extending the current list of acceptable counterions for PSs (11), and more than that toxicologically safe and already published liquid solvents (12) for solvates, up to the plentiful of neutral molecules as a coformers for PCCs, that are solids on ambient conditions and encompassed to the generally recognized as safe list (GRAS) and to even broader the everything added to food in the U.S. list (EAFUS), both regulated by the U.S. Food & Drug Administration (FDA) (13) in order counterions, solvents and conformers, each of them depending on each of their nature (molecular structure), when cocrystallize with API molecules to modulate the properties of native API. This conventional scientific approach for classification of the multicomponent crystals has been recognized as ambiguous by the academic and industrial community toward the vibrant debates aiming to contribute the upgrading of the definition for PCCs in the drafted FDA guidance, the first one issued in 2011 wherein PCCs are dissociable API-excipient molecular complexes of cocrystallized neutral API and conformer into solid drug product intermediates enforcing to comply to the requirements for current Good manufacturing Practice (cGMP), and consequently the second another, issued in 2016 that stipulates more comprehensively that PCCs are redefined as single crystalline materials composed by cocrystallized molecules of API and non-volatile conformer, bounded neither by nonionic, nor by noncovalent interactions, emphasizing that PCCs, instead of being recognized as the new API, their new phases to be considered as polymorphs or pseudopolymorphs (hydrates or solvate) of API. (14, 15) Though both regulatory authorities, US-FDA and European Medicines Agency (EMA) that are harmonized in terms of putting in evidence PCCs as single crystalline materials is a opportunity for disclosing the new solid phases of API toward their novelty, non-obviousness, utility and greenness as a prerequisite in process of patent protection of the unique composition and structure of solid state material. (16) Furthermore, the variety of conformers with diverse nature and properties, as a source is

**FIGURE 1:** The diversity of organic solid forms

utilized by crystal engineering that is a tool for designing crystal with purpose i.e. the conformer to influence the improvement of the particular and the desirable property of API, and as well to a cocrystal as new solid phase, entirely. The principle of co-crystallization refers to supramolecular chemistry phenomena of setup noncovalent intermolecular interactions (mainly all type of H-bonding, $\pi\bullet\bullet\pi$ stacking) that, either based on the homomeric molecular recognition between the same molecules, or heteromeric recognitions between different ones, such as API, conformer and solvent, lead to formation the basic structural units, known as synthons that are exist as homosynthons and heterosynthons when in the former the identical functional groups (moieties) interact by H-bonds and in later when H-bonding is occurred between different, but complementary proton donor-acceptor functional groups. (17–19) Referring to the nature of H-bond as electron donor-acceptor interactions (20) the charge distribution and

the extent of its transfer indicate to its significant partial distribution in some molecular crystals that overlap across both PCCs and PSs, representing cocrystal-salt continuum. In order to avoid overlapping across the PCs, PSs and Solvates, performed analyzes of the entries in the Cambridge Structural Database (CSD), based on the distinguishing charge location in salts from neutral conformers and solvents, and the number of cocrystallized component per asymmetric crystal cell (Z), impact the definitions for three classes of PCCs, PSs and Solvates to be expanded to additional four classes, that are in total seven mutually exclusive subclasses: true salt, true solvate, true cocrystal (binary systems, $Z^R = 2$), salt solvate, cocrystal solvate, cocrystal salts where neutral API cocrystallize with ionic conformer or salt form of API is cocrystallized with neutral coformer (ternary systems, $Z^R = 3$), and cocrystal salt solvate (quaternary systems, $Z^R = 4$), all relevant in terms of frequency of occurrence. (21) Moreover the

novelty of multicomponent systems (MCSs) rely on their appearance in form of the new solid crystalline phases, the nature of the noncovalent intermolecular interactions, determined by the molecular structures of APIs and conformers, and environmental conditions, rule the thermodynamic and kinetic stability of the solid phases during the opponent processes of cocrystallization and dissolving. Crystallographic analyses performed by both electron and neutron diffraction, indicated that extend of proton transfer in H-bonds depend on increasing the temperature. (22, 23) Therefore, X-ray diffraction on low temperature and cooper radiation on single crystals elucidate the proton position between the H-bond lengths formed by different proton doneor/acceptor groups, such C–O distance that is utile for distinguishing PSs from PCCs which components consisted of carboxylic acids. (24) Another approach for prediction of cocrystal formation, that is contributed by Etther's hydrogen bond rules (priorities for best H-bond donor/acceptor pairs) (25), is based on distinguishing cocrystals from salt and cocrystal salts based on the ΔpK rule: $\Delta pK = (\Delta pK_a - [pK_a(\text{conj. base}) - pK_a(\text{acid})])$; $\Delta pK_a \geq 3$ corresponds to salt formation (26), $\Delta pK_a < 0$ benchmark for cocrystal formation, while ΔpK_a values 0-3 imply for continuum of ambiguous prediction in cocrystal salts formation. (23, 27) Crystal engineering is challenging concept that utilizes systematic database study of structural landscape and high throughput crystal growth screening with crystallographic analyses of noncovalent interactions and structural parameters as a variables in determined structures that provide insight in optimizing the crystallization pathways that are designed strategies both for PCCs and PSs. (28)

Structure – Properties relationship: experimental vs. crystal structure prediction modeling

Crystal structure prediction (CSP) for PCCs and PSs, relaying on the quantum mechanical (QM) calculations for the crystal lattice energy for PCCs and PSs, indicates that the formation of these multicomponent crystals is determined by compromising either the negative enthalpy changes, always in enthalpy driven formation of PSs, as well in some PCCs and PCC solvates with entropy changes or positive enthalpy change for some entropically driven formation of PCCs, not always leading toward the free energy

minimization, that is due to propensity and propagation of heterosynthons to replace homosynthons, because of difference in energies of intra- and intermolecular forces that contribute the lattice energy. (29) This confirms the difference in the thermodynamic stability between PCCs and PSs comparing to their parent components and propose modeling for their crystal structure prediction to offer designing the accurate experimental crystallization screening strategies. (30–32) Though the computed energies of the crystals structures, ranged by the frequencies of synthons appearing within the CSD, reveal that at least 50% of the lattice energy is contributed by heterosynthons and to a few strong H-bonds between heterodimers and adjunct molecules, the higher energy value of supramolecular synthon carboxylic acid– pyridine(carboxylate/pyridinium, ionized coupled moieties) for PSs for ~ 10 kJ/mol, comparing for carboxylic acid – pyridine (neutral pair) confirmed the proton transfer that distinguishes PSs from PCCs. (30)Figure 2

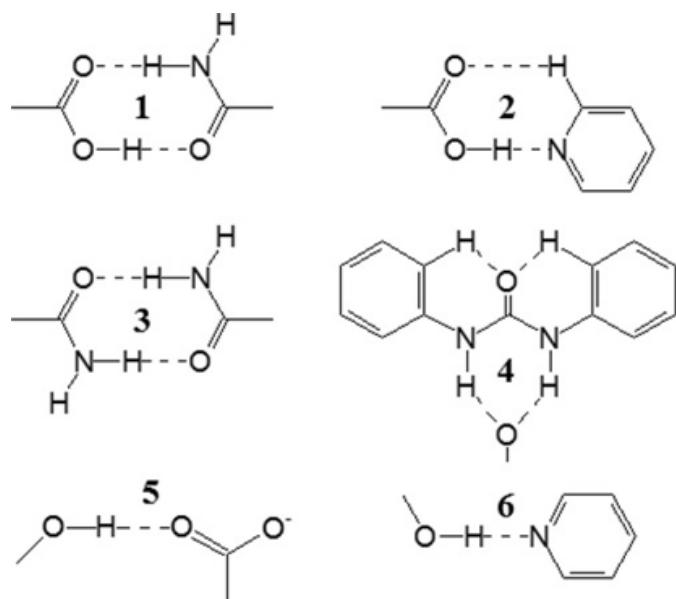


FIGURE 2: Supramolecular homo- and heterosynthons in CSD(Cambridge Structural Database): 1 Acid–Amide; 2 Acid–Pyridine; 3 Amide–Amide; 4 Diphenylurea Hydrate; 5 Hydroxyl–Acid; 6 Hydroxyl–Pyridine

Although recent theoretical and high pressure studies have shown that proton transfer in the pyridine-formic acid system is dependent on the amount of

formic acid present. (33, 34) Though the designing the successful cocrystal screening experiments is supported by strategies for selecting favorable coformers, the derived models, based on supplementary synthon strategy (35, 36), the criteria for shape and polarity descriptors (37), lattice energy (38, 39) and statistical analyses for knowledge-based PCCs prediction based on prevalence of occurring hydrogen bonds in relevant conformer structures in CSD (40, 41), so far lack accurate crystal structure prediction (CSP) (42). Recently, machine learning algorithm based on the molecular descriptors were tested for guiding the selection of coformers for a particular API in process of developing cocrystallization screening experiments. (43). Experimental data generated by single crystal x-ray diffraction analyses on the grown cocrystals of pharmaceutical compound phloroglucinol reveal the three OH groups of the phloroglucinol molecule are all involved in hydrogen bonds acting always as donors with three types of acceptor atoms: nitrogen (in most cases aromatic N), oxygen (carboxylic or hydroxilic) and O-atom from water molecules forming a cocrystals depicted on Figure 3 (44).

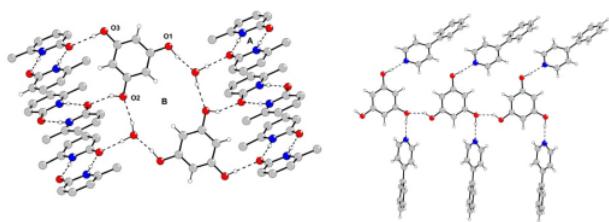


FIGURE 3: Motif of H-bonding interactions between phloroglucinol and N-heterocycles (44)

Though the large organic cations and anions, even when anions is conjugated base such it is sulfate, phosphate or chloride of the particularly strong inorganic acids, in PSs interact toward strong charge-assisted H-bonds (45, 46), theirs exposed polar functionalities with high hydration energy impact to additional stabilization toward the interaction with water. Charge-assisted H-bonds were detected in molecular salts of pyridoxine (vitamin B6) and hydroxylbenzoic acid derivatives with strong antioxidant activity, presented on Figure 4 . (47)

This uptake of water as solvent or from highly humid atmosphere may cause either deliquescence

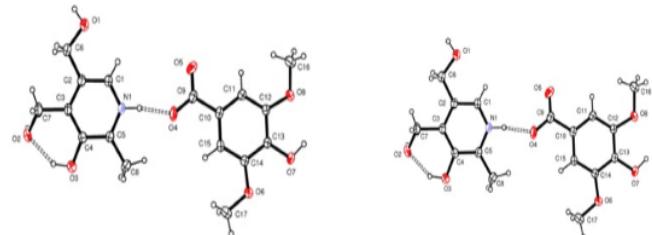


FIGURE 4: Motifs of Charge-assisted H-bonds between pyridoxonium cation and carboxylated anions in molecular salt of Pyridoxine (vitamin B6) (47)

of salt, forming form high concentrated solutions unable to crystallize under ambient temperature and humidity, or to form crystalline salts hydrates within water polar molecules with metal cation cocrystallize in stoichiometric ration along exposed crystal faces. (48, 49) Calculated lower lattice energy for majority of cocrystals then the values for the sum of their components lattice energies, imply to higher thermodynamic stability and more feasible cocrystal formation. (30, 39, 50)

Conclusion and perspective for further research on pharmaceutical crystalline solids

PCC and PSs offer the opportunities for beneficial therapy outcomes if API cocrystallize with conformers or salt formers that lead to formation of multicomponent crystals that structure influence alternated particle habits and size, consequently that tune their hydroscopicity, processability, thermodynamic and photostability, and modulate both its thermodynamic and kinetic solubility up to extent of plasma concentration that suits the therapeutic index. (51) The emergency for understanding solid-state control, selection and properties in late stage of drug discovery and NEC (New Chemical Entity) drug development obeys Quality by Design (QbD) concept that is proposed within to scientifically proven ICH Q8(R2) guideline. (52) Machine learning concept, based on the Artificial Neuron Networks (ANN) is developed for prediction of solid state properties of cocrystals (melting points, lattice energy and crystal density). (53)

Engineering multidrug cocrystals (54) has become viable platform for overcoming the drawbacks of

conventional formulations for fixed-doses combination (FDC) such it is multi-drug resistance and adverse and side effects. (55) Furthermore, the advantage of formulating multidrug cocrystals should be expected to attenuate or enhance the drug action synergistically by rational selection of combined drugs, more convenient to get compliance and adherence in therapy, to reduce the copayment cost for patients, and to support the market exclusivity that, due to patentable formulation, implies the improvement in sales and profits for pharmaceutical companies. (54, 56).

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