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Cocrystals to facilitate delivery of poorly soluble compounds beyond-rule-of-5☆

Gislaine Kuminek [a], Fengjuan Cao [a], Alanny Bahia de Oliveira da Rocha [b], Simone Gonçalves Cardoso [b], Naír Rodríguez-Hornedo [a,*]

[a] Department of Pharmaceutical Sciences, University of Michigan, Ann Arbor 48109-1065, MI, USA
[b] Programa de Pós-Graduação em Farmácia, Universidade Federal de Santa Catarina, Florianópolis 88040-900, SC, Brazil

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ABSTRACT

Besides enhancing aqueous solubilities, cocrystals have the ability to fine-tune solubility advantage over drug, supersaturation index, and bioavailability. This review presents important facts about cocrystals that set them apart from other solid-state forms of drugs, and a quantitative set of rules for the selection of additives and solution/formulation conditions that predict cocrystal solubility, supersaturation index, and transition points. Cocrystal eutectic constants are shown to be the most important cocrystal property that can be measured once a cocrystal is discovered, and simple relationships are presented that allow for prediction of cocrystal behavior as a function of pH and drug solubilizing agents. Cocrystal eutectic constant is a stability or supersatuation index that: (a) reflects how close or far from equilibrium a cocrystal is, (b) establishes transition points, and (c) provides a quantitative scale of cocrystal true solubility changes over drug. The benefit of this strategy is that a single measurement, that requires little material and time, provides a principled basis to tailor cocrystal supersaturation index by the rational selection of cocrystal formulation, dissolution, and processing conditions.

Contents

Abbreviations: RCM, Reaction crystallization method; PSD, Phase solubility diagram; FeSSIF, Fed state simulated intestinal fluid; $[drug]_{eu}$, Drug concentration at the eutectic point; $[coformer]_{eu}$, Coformer concentration at the eutectic point; K_{eu}, Eutectic constant, $K_{eu} \equiv [coformer]_{eu}/[drug]_{eu}$; $S_{cocrystal}$, Cocrystal solubility; S_{drug}, Drug solubility; $S_{coformer}$, Solubility of coformer; S_T, Total solubility in media with solubilizing agents, $S_T = S_{aq} + S_s$; S_{aq}, Aqueous solubility at a given pH, $S_{aq} = S_{nonionized,aq} + S_{ionized,aq}$; $S_{cocrystal,aq}$, Cocrystal solubility in aqueous media; $S_{cocrystal,T}$, Total cocrystal solubility in solubilizing agent media; $S_{drug,aq}$, Drug solubility in aqueous media; $S_{drug,T}$, Total drug solubility in solubilizing agent media; pH_{max}, pH at which both drug and cocrystal have equal solubilities; CSC, Critical stabilization concentration; S^*, Solubility at which both drug and cocrystal have equal solubilities; SR, Solubilization ratio, $SR = S_T/S_{aq}$; $SR_{cocrystal}$, Cocrystal solubilization ratio, $(S_T/S_{aq})_{cocrystal}$; SR_{drug}, Drug solubilization ratio, $(S_T/S_{aq})_{drug}$; SA, Cocrystal solubility advantage, $SA = S_{cocrystal}/S_{drug}$; CMC, Critical micellar concentration; K_{sp}, Solubility product; K_s, Solubilization constant; K_a, Dissociation constant; [M], Micellar surfactant concentration; $\frac{dc}{dt}$, Dissolution rate; J, Flux (mass/surface area/time); D, Diffusion coefficient; S, Equilibrium solubility; A, Surface area of solid drug; h, Thickness of diffusion layer; pH_0, Microenvironment pH; pH_{bulk}, Bulk solution pH.

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* Corresponding author.

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1. Introduction

Cocrystals have emerged as a means of fine-tuning solubility, dissolution, bioavailability, and other physicochemical properties of drug substances, without changing their molecular structure. Cocrystals are a class of multicomponent solids containing two or more different molecular components in a single homogenous crystalline phase with well-defined stoichiometry [1–5]. They are distinguished from solvates in that the cocrystal components are solids at room temperature.

Hydrogen-bonded assemblies between the neutral molecules of the drug and the cocrystal coformer often guide cocrystal formation [2,4], which is why they are of particular interest due to their ability to modify the solubility properties of nonionizable drugs that cannot otherwise form pharmaceutical salts. Over the last decades cocrystals have received significant attention from the pharmaceutical industry, and numerous pharmaceutical cocrystals have been reported. A pharmaceutical cocrystal is composed of an active pharmaceutical ingredient (API) and a benign molecule or other APIs as coformers. Coformers are commonly selected from substances appearing on the GRAS (generally regarded as safe) status list or those that have been demonstrated to be non-toxic and have regulatory approval [6,7].

Physicochemical criteria, such as those defined by the Lipinski rule of five, are typically used to predict whether lead molecules, frequently found from high throughput or biological screening, will become drug candidates with adequate permeability, solubility, and bioavailability. Drugs that are highly permeable, are lipophilic and often exhibit poor aqueous solubility [8].

Solid-state modifications and formulation design allow for the improvement of the physicochemical properties of a drug substance while maintaining the same chemical entity and pharmacological interaction. Polymorphs, solvates and salts are the common solid forms employed for product development. However, consideration of cocrystals and cocrystalline salts as viable solid forms for development would significantly expand the number and diversity of solid drug forms available, and improve the likelihood of finding a solid form with the required physicochemical properties [9]. A schematic representation of the different classes of multicomponent solids is shown in Fig. 1.

Unlike salts, cocrystals do not rely on ionic interactions and cocrystals can be made for non-ionizable drugs. Also, for cocrystal formation the number of suitable coformers can exceed the number of suitable counterions for salt formation. In contrast to amorphous pharmaceutical forms, cocrystals can achieve thermodynamic stability in the solid state while providing large solubility advantage over a drug. Compared to polymorphs, cocrystals have the ability to increase solubility by orders of magnitude above the drug solubility.

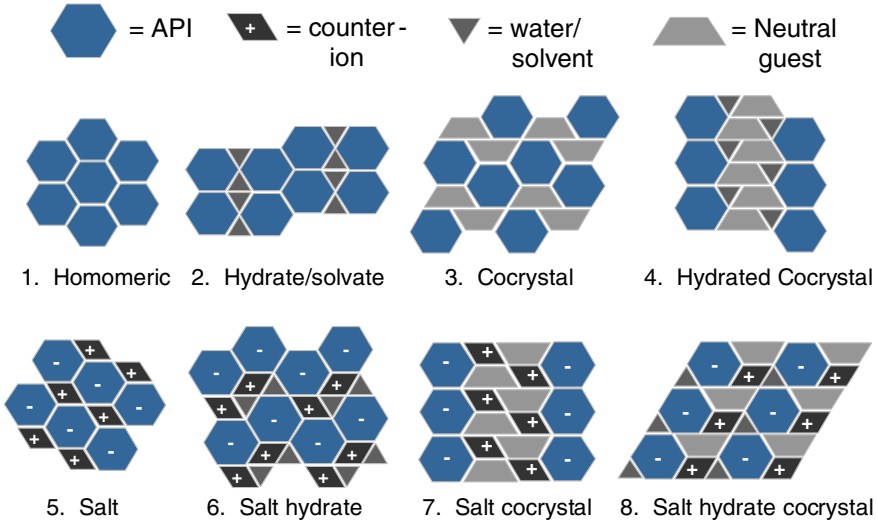

Fig. 1. Comparison of multicomponent solid form modifications that can be used to alter the properties of a drug [10]. Reproduced with permission of the American Chemical Society (http://pubs.acs.org/doi/pdf/10.1021/cg900129f).