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Mini Review

Mitigating Cocrystal Physical Stability Liabilities in Preclinical Formulations

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ABSTRACT

Poor aqueous solubility of a majority of new small molecule chemical entities is a significant challenge in drug discovery since considerably high exposures are often required to enable pharmacokinetic, pharmacology, and toxicology studies. Pharmaceutical cocrystals have received considerable attention in recent years owing to their potential to improve the physicochemical properties and *in vivo* performance of poorly soluble drugs. However, physical instability in supersaturated solution/suspension formulations is a major concern for their use in preclinical studies. This review will present an overview of the thermodynamic and kinetic contributions impacting physical stability of cocrystals in preclinical formulations with a focus on the role of surfactants, polymeric excipients, and pH. Finally, the *in vivo* performance of cocrystals will be discussed. The article will conclude with a perspective on strategies to develop physically stable preclinical cocrystal formulations.

Introduction

Over the last 20 years, drug candidates with poor aqueous solubility and dissolution rate have become more prevalent, often leading to suboptimal exposure in toxicology and clinical studies, and even candidate failure if the problem is not rectified.[1,2] In addition to classical phase and formulation methods,[3] new complimentary methods such as the cocrystal approach[4] are frequently introduced to mitigate the challenges of solubility and dissolution-limited absorption. As recently reviewed, several pharmaceutical cocrystals case studies have been published within the last 10 years, demonstrating improved physicochemical properties and pharmacokinetics (PK).[4-8] A pharmaceutical cocrystal is a multicomponent crystal, held together by nonionic/noncovalent forces, wherein at least 1 component is an active pharmaceutical ingredient (API).[4] Table 1 shows a classification scheme of solid multicomponent phases including the definition of cocrystals used in this article.

The strategy set for phase discovery impacts the overall success rate for pharmaceutical cocrystals. It has been suggested to use the Cambridge Structural Database to understand and predict hydrogen bond formation in the parent free form.[4,9] These data could also be used to strategically incorporate classical and novel reliable hydrogen bond donors and acceptors in a particular chemical series during drug discovery to further increase the success rate. Cocrystal former selection is equally important, and pharmaceutically acceptable counterions (salts) and coformers (cocrystals) are generally selected from the same list. The primary criterion used to define coformer acceptability is the availability of sufficient toxicology data to warrant safe use at targeted doses (see the references[10,11] for a listing of potential counterions). Equally important is of course the ability to form a cocrystal, and phase screening is generally an empirical process and often carried out in a high-throughput fashion.[12] As discussed in detail later in the article, cocrystals have complex phase diagrams and the phase discovery stage of a program may lead to fewer cocrystal hits unless the region is encountered where a cocrystal is stable. To increase the number of hits without decreasing throughput, diversifying screening technologies (e.g., incorporating solid and solvent drop grinding or melt crystallization) may prove useful.[9,13] In addition, varying the coformer ratio or selecting solvents based on parent free form and coformer solubility can increase the probability of empirically encountering the region of the phase diagram where cocrystal is stable.

Even after a cocrystal with desired pharmaceutical attributes of improved solubility and dissolution rate is identified, physical instability (conversion to individual cocrystal components) is a key liability, and no or at least controllable phase conversion is desired. A recent review found a relationship between physical stability and

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Table 1
Classification of Solid Multicomponent Phases

Forces Holding Components Together or Physical State of Guest	Liquid at RT	Solid at RT
Ionic	Salt	Salt
Nonionic or covalent such as hydrogen and Van der Waals, etc.	Solvate or hydrate	Cocrystal

RT, room temperature.

coformer solubility in aqueous slurries. Accordingly, coformers with <10 mg/mL water solubility gave rise to cocrystals with better physical stability.[4] As discussed later in detail, the physical instability problem is primarily prevalent in solutions or slurries, and many pharmaceutical cocrystals are stable in the solid state.[4] However, solution or suspension formulations are generally required for rodent and nonrodent toxicology studies, with sufficient stability required to allow for preparation and dosing of the cocrystal form. Lohani et al.[14] recently published 6 h as an absolute minimum physical stability window. However, while this is feasible for daily formulation preparations, it could be logistically challenging for longer term development toxicology studies. This review primarily focuses on the physical stability of cocrystals. The main objective of this review was to evaluate and combine the available approaches and concepts and propose a practical strategy to come up with stable preclinical formulations for cocrystals. Kinetic and thermodynamic factors impacting the physical stability of a cocrystal in preclinical formulations and its *in vivo* performance will be discussed in detail. This will be followed by a summary and discussion of the different stabilization strategies proposed in the literature for cocrystal formulations and the authors' perspective on a comprehensive stabilization strategy.

Physical Stability of Pharmaceutical Cocrystals in Solution and Suspensions

Presence of water combined with a high drug load requirement in preclinical formulations can result in high supersaturation levels which can in turn lead to accelerated conversion of a metastable cocrystal back to the stable parent free form.[4,7,15] As in case of the amorphous form or other supersaturating drug delivery systems, this phase change may lead to the loss of improved apparent solubility/dissolution rate and bioperformance. This conversion is thus undesirable. Given this relationship to bioperformance, it is important to investigate the physical stability of pharmaceutical cocrystals in aqueous formulations. Only a few pharmaceutical cocrystals have reached preclinical and clinical development and have been published in the scientific literature. Hence, limited stability information in aqueous formulations (i.e., with excipients) is available at this time, but examples of cocrystal physical stability in unformulated aqueous solutions and slurries (without excipients) will be used to illustrate the issue of physical instability in preclinical formulations.

In an intrinsic dissolution study of the glutaric acid cocrystal of a sodium channel blocker, McNamara et al.[16] observed a slight conversion to the parent free form after 90 min and full conversion after 24 h. This was in contrast to the solid state, where the cocrystal only adsorbed 0.08% moisture at 95% relative humidity (RH). The cocrystal was also stressed at 60°C and 40°C/75% RH for 2 months without any change in the solid state.[16] In another study, 14 of 20 cocrystals (mostly more soluble than the free form) of AMG 517 reverted to the free base hydrate within 24 h of the fasted-state simulated intestinal fluid (FaSSIF) solubility experiment. As expected, minimal or no conversion was observed in cocrystals which were less soluble than AMG 517 free form. However, in the solid state, all the cocrystals were either slightly or nonhygroscopic, and no conversion was seen in the stressed physical stability study at 40°C/75% RH after 1 month.[17,18] Thus, physical stability can be significantly reduced in the presence of aqueous media.

Another example of cocrystal instability in an aqueous environment was provided by Sanphui and Rajput[19] who reported several cocrystals of hydrochlorothiazide with nicotinic acid, nicotinamide, succinamide, p-aminobenzoic acid, resorcinol, and pyrogallol. Only the p-aminobenzoic acid cocrystal showed stability up to 24 h in aqueous medium, while other cocrystals rapidly converted back to hydrochlorothiazide within 1 h of the dissolution experiment and only afforded a nominal solubility improvement over HCT. Childs et al.[20] prepared cocrystals of fluoxetine hydrochloride (active ingredient in Prozac®) with benzoic acid, succinic acid and fumaric acid, wherein benzoic acid and fumaric acid cocrystals exhibited slower dissolution than the parent free form. Only the succinic acid cocrystal, which provided a drastic improvement in solubility and dissolution rate, was observed to revert back to fluoxetine hydrochloride in the powder dissolution experiment. These findings highlight the physical instability liability of a metastable cocrystal in an aqueous environment. Another study of a carbamazepine saccharin cocrystal revealed a small amount of overnight conversion to the carbamazepine dihydrate in dissolution media when large particle size material was used (i.e., 500 μm to >1 mm).[21] Material with smaller particle sizes (i.e., <500 μm) was resistant to the reversion and also improved the dissolution rate significantly. Authors hypothesized that, in addition to the particle size effect, this physical instability on the surface of the larger crystals might be contributing to the lower carbamazepine concentrations. These are just a few of many examples of physical instability in aqueous solutions and slurries and highlight the challenges in developing stable preclinical formulations of cocrystals.

Physical Stability of Pharmaceutical Cocrystals—Thermodynamic Considerations

Equilibrium physical stability of a cocrystal is intimately linked to its thermodynamic solubility.[22-25] While kinetic physical stability of a cocrystal may be practically more relevant to bioperformance, the equilibrium stability information can enable the differentiation of the thermodynamic and kinetic factors, which can lead to a better understanding and control of the kinetic stability behavior and feed into design of better cocrystals and stable preclinical formulations.[26]

Thermodynamic stability and solubility behavior of a cocrystal can be described by an isothermal ternary phase diagram, which outlines the phase relationships of the free form and the coformer at different concentrations in a solvent.[22-25,27] Similar to the concepts developed for sparingly soluble salts, models based on cocrystal formation and dissociation equilibria have been developed to describe these phase relationships.[25] Figure 1 shows such a ternary phase diagram wherein different regions (marked by numbers) represent the stability domains of different components (free form, coformer and the cocrystal). An important characteristic of these phase diagrams is the existence of cocrystal eutectic points (E1 and E2) which represent the 3-phase equilibrium between 2 solid phases (cocrystal and either parent free form or coformer) and the solution phase. Good et al.[28] reported that these eutectic points can be used to characterize cocrystal solubility and physical stability behavior. They exemplified it further by developing models to calculate the cocrystal solubility profile using the eutectic concentrations of the individual cocrystal components for several cocrystal systems. These eutectic concentrations—based solubility