CO-CRYSTALS: AN EMERGING APPROACH FOR ENHANCING PROPERTIES OF PHARMACEUTICAL SOLIDS

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SUMMARY

Formulation of drug products is a multidisciplinary field, with pharmaceutical materials science being a fundamental branch that continuously provides important insights, theories, and technologies to formulation sciences. The recent advances in this area have brought the possibility to produce pharmaceutical materials by design. In particular, the formation of co-crystals, i.e. crystalline molecular complexes of two- or more neutral molecules, represents a potential route to achieve pharmaceutical materials with improved properties of interest, including dissolution rate and stability under conditions of high relative humidity. As an additional solid state form of active pharmaceutical ingredients (APIs), co-crystals not only offer a tool for tailoring physicochemical properties, but also create new opportunities for the research-based pharmaceutical companies to address intellectual property (IP) protection issues. At the same time, co-crystals presents new challenges for the pharmaceutical industry, primarily related to their design and screening. This review introduces co-crystals as an emerging class of pharmaceutical materials, focusing on the experimental methods applicable to their screening. In addition, the examples illustrating how the co-crystal approach can be utilized to enhance the specific properties of pharmaceutical solids, such as dissolution rate of poorly-water soluble APIs and physical stability of moisture-labile APIs, are presented.

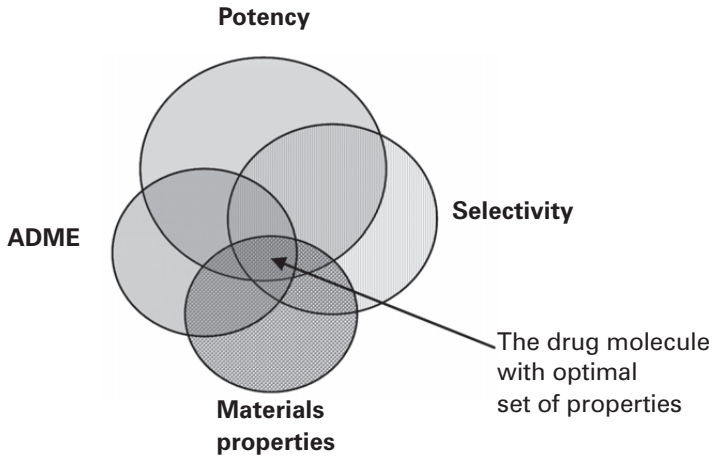

Figure 1. A simplified schematic overview of the properties vital for a successful drug candidate (adapted from Gardner et al 2004).

INTRODUCTION

The ability to deliver the drug to the patient in a safe, efficient and cost-effective manner depends largely on the physicochemical properties of the active pharmaceutical ingredient (API) in the solid state, as schematically illustrated in **Figure 1**. This provides a significant driving force for inventing new approaches to designing pharmaceutical solid materials with specific physicochemical properties. In the last years, crystal engineering of APIs through co-crystallization has gained an increased interest as means of optimizing the physical properties and/or stability of solid dosage forms (Almarsson and Zaworotko, 2004).

Co-crystals can be defined as crystalline complexes of two or more neutral molecular constituents bound together in the crystal lattice through noncovalent interactions (primarily hydrogen bonding) (**Figure 2**). The formation of pharmaceutical co-crystals involves incorporation of a given API with another pharmaceutically acceptable molecule in the crystal lattice. The resulting multi-component crystalline phase will maintain the intrinsic activity of the parent API

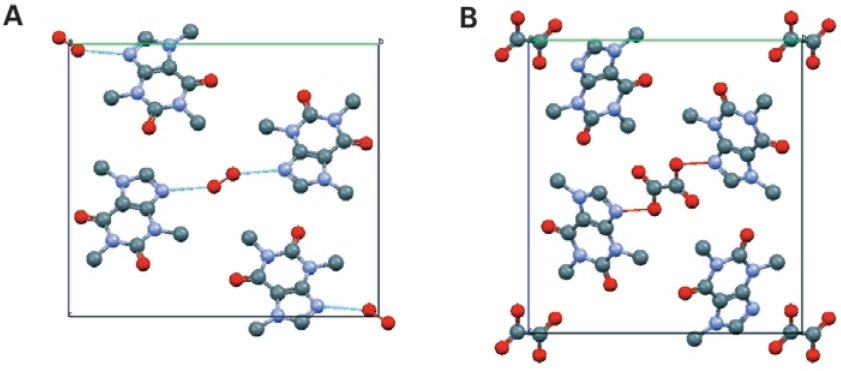

Figure 2. Example of two-component caffeine crystals, the monohydrate (A) and the co-crystal with oxalic acid (B). The unit cells of the crystals viewed along the a-axis are shown. The hydrate incorporates the solvent (water) molecule in the crystal lattice, while the co-crystal consists of two solid compounds. Note that in both structures, the same hydrogen bridges (shown by dotted lines) are involved to connect the host (caffeine) with guest (water or oxalic acid) molecules.

while possessing a distinct physicochemical profile. The key benefits associated with co-crystallization approach to modifying properties of pharmaceutical solids are the theoretical capability of all types of drug molecules, including weakly ionizable and non-ionizable, to form co-crystals, and the existence of numerous potential counter-molecules, including food additives, preservatives, pharmaceutical excipients as well as other APIs, for co-crystal synthesis (Vishweshwar et al 2006). Additional valuable advantages that co-crystal formation may offer for the pharmaceutical industry are the opportunity of intellectual property (IP) protection and the possibility of extending the life cycles of old APIs.

This article outlines co-crystals as an emerging class of pharmaceutical materials, focusing on experimental methods applicable to their screening and the examples illustrating how the co-crystal approach can be utilized to enhance the specific properties of pharmaceutical solids such as dissolution rate of poorly-water soluble APIs and physical stability of moisture-labile APIs.

CO-CRYSTAL SCREENING

The ultimate goal of co-crystal screens is to discover a solid form of an API with improved physical properties. From this perspective, an efficient co-crystal screening protocol can be split into three phase: (1) co-crystal design; (2) co-crystal screening and (3) co-crystal selection. A general guideline for co-crystal screening is schematically presented in **Figure 3**.

A distinguishing feature of co-crystals, as compared to other crystalline forms of APIs, is that these multicomponent systems are susceptible to design by crystal engineering (Vishweshwar et al 2006; Blagden et al 2007). Consequently, an important initial step in co-crystal screening is the selection of co-crystal formers from supramolecular libraries of co-crystallizing agents (Otto and Sander 2004). Like in polymorph screens, the major experimental techniques to generate co-crystals are solution-based crystallization methods (Zhang et al 2007), especially solvent evaporation and slurry conversion. It should be emphasized, however,

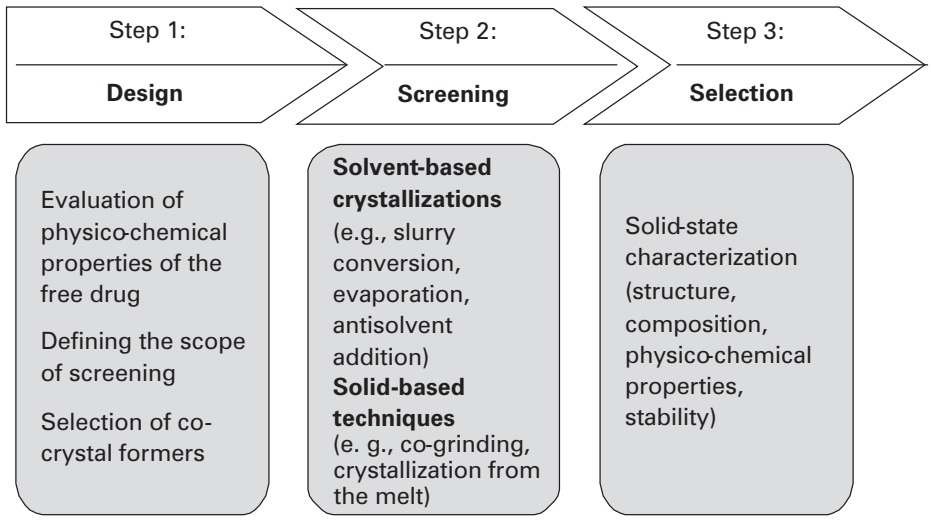

Figure 3. A general guideline for co-crystal design and screening.

that solid-based approaches (e.g., neat grinding and liquid-assisted grinding) have been proved to be a viable synthetic method for pharmaceutical co-crystals (Etter et al 1993, Caira et al 1995, Kuroda et al 2002, Trask et al 2004). Moreover, in a number of instances co-crystal synthesis by employing solid-based techniques offers enhanced selectivity as compared with that of solution crystallization. For example, in a model system of co-crystals with caffeine and several monocarboxylic acids, neat grinding generated polymorphs, which were initially inaccessible from solution (Trask et al 2005). Liquid-assisted grinding (Karki et al 2007) involves co-grinding of two or more materials with the addition of a minor quantity of solvent, which plays a catalytic role and thus further enhances selectivity of the solid-state synthesis.

In the final stage of the screen, the co-crystals are characterized and their properties are compared with other possible solid state forms (free API, salt, hydrate) to ensure that the best form will be selected for further development.

CO-CRYSTALLIZATION AS A TOOL FOR PHYSICAL PROPERTIES OPTIMIZATION OF PHARMACEUTICAL SOLIDS

The main motivation to explore co-crystals of pharmaceuticals is to potentially modify their physical properties, primarily dissolution rate (and hence bioavailability) and hygroscopicity/physical stability. Hence, this section highlights co-crystallization as a tool for enhancing these specific properties of APIs.

With the advent of combinatorial chemistry, API possessing limited aqueous solubility (Biopharmaceutics Classification System Class II drugs) are becoming increasingly prevalent in the research and developments portfolios of pharmaceutical companies. The challenging aspects in development such drug molecules are associated with their slow dissolution in biological fluids and thus insufficient and inconsistent systemic exposure, and consequent sub-optimal clinical efficacy. The traditional approaches (e.g., salt formation, micronization, solid dispersion formulations) to address the issues of poor aqueous solubility often fail to produce a viable solid form as the achieved increase in dissolution rate is insufficient to provide adequate enhancement of bioavailability (Blagden et al 2007). In this context, pharmaceutical co-crystals as a distinct solid phase possessing the unique set of properties can be the advantageous alternative to the other solid-state modification techniques. The vivid example demonstrating the success of the co-crystal approach to enhance dissolution rate of APIs is an extremely water-insoluble antifungal agent itraconazole. Remenar and collaborators (2003) have shown that the co-crystals of itraconazole with various carboxylic acids exhibit a higher solubility and a faster dissolution rate in comparison with those for the free base. Moreover, the dissolution profile of co-crystals with L-malic acid has matched that of the commercial product (Sporanox) containing amorphous itraconazole.

The stability of a solid API over a wide range of relative humidities is another essential aspect within the pharmaceutical industry as it has practical implications for processing, formulation, packaging, and storage (Khankari and Grant 1995, Byrn et al 1999). It is often the case that moisture promotes unwanted solid phase transformations of an API (polymorphic transformations, hydrate formation or crystallization of amorphous phase) (Airaksinen et al 2005, Jorgensen et al 2006, Mirza et al 2007), which may compromise drug product safety and bioavailability (Morris et al 2001, Byrn et al 1999). One approach proposed to inhibit such moisture-induced phase-transformations is rational excipient selection for a specific formulation (Airaksinen et al 2005). In this context, co-crystallization of an API with an excipient can be thought as a more radical strategy to address the issues of poor physical stability of moisture-sensitive pharmaceutical materials. For instance, the caffeine/oxalic acid co-crystals have been demonstrated to be superior to caffeine anhydrate in terms of physical stability to humidity (Trask et al 2005). Also, an ongoing study in our laboratory demonstrates that co-crystal formation of theophylline with capric or stearic acid can be a promising approach to enhance physical stability of this moisture-labile API (Mirza S, unpublished observation 2008). Some other examples of pharmaceuticals co-crystals reported in the literature are presented in **Table 1**.

Table 1. Selected examples of pharmaceutical co-crystals systems reported in the literature

API	Co-crystal former	Preparation method	Enhanced property (if reported)	Reference
Aspirin	4,4'-Dipyridil	Slurry conversion		Walsh et al 2003
Caffeine	Oxalic acid Glutaric acid	Solvent-assisted grinding	Physical stability	Trask et al 2005
Carbamazepine	Nicotinamide Saccharin	Cooling crystallization	Physical stability, dissolution rate and oral bioavailability	Hickey et al 2007
Fluoxetine hydrochloride	Benzoic acid Succinic acid Fumaric acid	Solvent evaporation	Intrinsic dissolution rate	Childs et al., 2004
Flurbiprofen	4,4-Dipyridyl	Solvent evaporation		Oberoi et al 2005
Ibuprofen	4,4-Dipyridyl Nicotinamide	Solvent evaporation	Solubility	Walsh et al 2003; Oberoi et al 2005
Indomethacin	Saccharin	Solvent evaporation or solvent-assisted grinding	Physical stability and dissolution rate	Basavoju et al 2008
Itraconazole	Malic acid Tartaric acid Succinic acid	Solvent evaporation	Improved dissolution rate	Remenar et al 2003
Norfloxacin	Isonicotinamide Succinic acid Malonic acid Maleic acid	Solvent evaporation	Solubility	Basavoju et al 2006
Paracetamol	4,4-Dipyridyl	Solvent evaporation		Oswald et al 2004
Piroxicam	Saccharin	Solvent evaporation		Childs et al 2007

SUMMARY

Co-crystals, molecular complexes of an API with one or more solid components, is an emerging class of pharmaceutical materials that are susceptible to design by crystal engineering. This implies that the functional properties of APIs (e.g., solubility and physical stability) can potentially be built-in during the solid-state synthesis. In this context, the selection of a relevant co-crystal former becomes a crucial issue and requires creating supramolecular libraries of co-crystallizing agents. A further challenging aspect is related to the development of efficient co-crystal screening technologies. As a rule, the solid-based techniques, such as neat grinding and liquid-assisted grinding, tend to demonstrate a higher selectivity, as compared to solvent-based approaches, in revealing the co-crystallization potential between multiple molecular species. From physical properties perspective, a key advantage of co-crystals as a solid form of an API is the possibility of achieving the high dissolution rate comparable to that of the amorphous form, while maintaining the long-term chemical and physical stability that crystalline forms provide. Finally, an important legal aspect associated with co-crystals is the opportunity for the research-based pharmaceutical companies to significantly expand their intellectual property portfolios.

TIIVISTELMÄ

Sekakiteet, molekyylitason lääkeaineen ja yhden tai useamman muun komponentin kompleksit, ovat uusi farmaseuttisten materiaalien ryhmä jossa hyödynnetään kidetilan suunnittelua. Lääkeaineen toiminnalliset ominaisuudet (esimerkiksi liukoisuus ja fysikaalinen säilyvyys) voidaan suunnitella jo kiinteän tilan synteesivaiheessa. Tässä tapauksessa relevantin sekakiteen muodostajan valinta on kriittinen, ja siinä joudutaan hyödyntämään sekakiteissä käytettävien aineiden tietokantoja. Toinen haaste on sekakideseulontateknologioiden kehittäminen. Kiinteään tilaan perustuvat teknologiat kuten jauhaminen kuivana ja nesteessä antavat yleensä paremman selektiivisyyden kuin liuottimiin perustuvat menetelmät. Näin saadaan selville useammalle molekyylille sekakiteiden muodostusmahdollisuudet. Fysikaalisten ominaisuuksien näkökulmasta lääkeaineen sekakiteiden päähyöty on niiden nopeampi liukoisuusnopeus joka on verrattavissa amorfisen muodon liukoisuusnopeuteen, mutta säilyttäen kiteisen muodon hyvän pitkän aikavälin kemiallisen ja fysikaalisen säilyvyyden. Lisäksi, sekakiteet antavat lääkeyrityksille mahdollisuuden laajentaa patenttikokoelmiaan.

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