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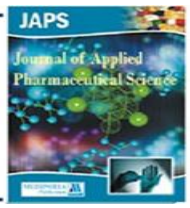

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New Trends in the Co-crystallization of Active Pharmaceutical Ingredients

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ABSTRACT

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. Co-crystals consists of API and a stoichiometric amount of a pharmaceutically acceptable co-crystal former. Pharmaceutical co-crystals are nonionic supramolecular complexes and can be used to address physical property issues such as solubility, stability and bioavailability in pharmaceutical development without changing the chemical composition of the API. These can be constructed through several types of interaction, including hydrogen bonding, pi-stacking, and van der Waals forces. Phase transformations induced during processing/storage affects the mechanisms of conversion of crystalline drugs to co-crystals. Pharmaceutical co-crystals considered better alternatives to optimize drug properties could play a major part in the future of API formulation and can be employed for chiral resolution. This review introduces co-crystals as an emerging class of pharmaceutical materials, focusing on the experimental methods applicable to their crystallization. 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.

Keywords: Co-crystal; API; Phase transformations; Supramolecular complexes; Physical stability.

INTRODUCTION

Cocrystals are at present the most dynamically developing group of solid pharmaceutical substances. The definition of the term “pharmaceutical cocrystal” is still under discussion, but essentially it is a multi-component compound that is formed between a molecular or ionic API and a cocrystal former that is a solid under ambient conditions (Vishweshwar, 2006). Pharmacodynamically, cocrystal former is a ballast molecule (the same applies to salts), and the GRAS rules apply. Nevertheless even a cocrystal former can be an active molecule. The stoichiometric ratio of API and cocrystal former in a pharmaceutical cocrystal is mostly simple (1:1, 1:2, 1:3 or vice versa). Cocrystals are not necessarily binary compounds, ternary and quarternary cocrystals are known. Cocrystals can be divided into: cocrystal anhydrates, cocrystal hydrates (solvates), anhydrates of cocrystals of salts and hydrates (solvates) of cocrystals of salts. The borderline between salts and cocrystals is blurred and can be distinguished by the location of

the proton between an acid and a base. In salts, carboxyl proton is moved to the hydrogen of the base while in cocrystals the proton remains on the 5 carboxyl of the acid. In cases when D pKa = pKa (base) – pKa (acid) = 0 – 3, the transfer of proton is ambiguous and we talk about the salt-cocrystal continuum (Childs and Stahly, 2007).

The cocrystallization potential of some active molecules is studied in detail, e.g.carbamazepine, itraconazole, piroxicam, norfloxacin, fluoxetin, caffein and others (Schultheiss and Newman, 2009). The reason is to achieve a wide variation in solid-state properties of APIs. These efforts stem from principles of supramolecular chemistry and crystal engineering to affect the properties of API through the "bottom up" approach. This is illustrated in the following examples. By the cocrystallization of antifungal drug itraconazole with 1, 4-dicarboxylic acids (succinic acid, L-tartaric acid or L-malic acid) a modification of the dissolution profile is achieved compared to the amorphous form of itraconazole (Sporanox, Janssen-Cilag) (Morissete *et al.*, 2004). A 1:1 carbamazepine/saccharin cocrystal compared to polymorph III of carbamazepine (Anticonvulsant Tegretol, Novartis) shows no polymorphous behaviour and is not prone to hydration (Morissete *et al.*, 2007). The cocrystallization of pregabalin with S- mandelic acid separates from the mixture of R and S isomers only the (1:1) cocrystal (S)-pregabalin/(S)-mandelic acid. This technology is used by Pfizer in manufacturing daosage form Lyrica (Zaworotko M, 2008). The cocrystals of paracetamol show improved tablet formation ability than free paracetamol, polymorph I (Panadol, GlaxoSmithKline) (Jones, 2009). Caffein tends to form hydrates at high RH (relative humidity) while its cocrystals with oxalic acid or malonic acid do not have this unwanted property (never form hydrates) (Jones, 2009). However, general trends of variation of properties during the transition from APIs to their cocrystals are not so far evident because fundamental causes of cocrystallization are not known so far. The preparation of cocrystals involves a number of techniques, in gas, liquid or solid phase. The most important is the joint cocrystal growth from solution or joint solid state grinding.

Often with the addition of a small amount of a "molecular lubricant" (methanol, cyclohexan, chlorophorm etc.). Furthermore, co-crystals can be synthesized by evaporation, sublimation, melting, sonication etc. It often holds that identical starting components may not yield the same product under different cocrystallization techniques. Although cocrystals are intensively studied and patented by both academic institutions and R&D departments of pharmaceutical companies, there is no medicament on the market formulated from a cocrystal. Nevertheless it turns out that some pharmaceutical salts should be re-classified as co-crystals. This is also important for patent litigation.

Polymorphs, solvates, salts, and co-crystals are schematically depicted in Fig. 1. We will use the term "drug substance" for the therapeutic moiety, which may be a solvate, salt or a co-crystal, while the single, uncharged molecule will be called the "active molecule.

The brief chronological scheme outlines the progress of crystal engineering during the last 50 years, and more so since the late 1980s from when onwards the attention of the chemical community has become more fully focused on it. The work of Schmidt on topochemistry is considered by many to represent the formal beginnings of crystal engineering.

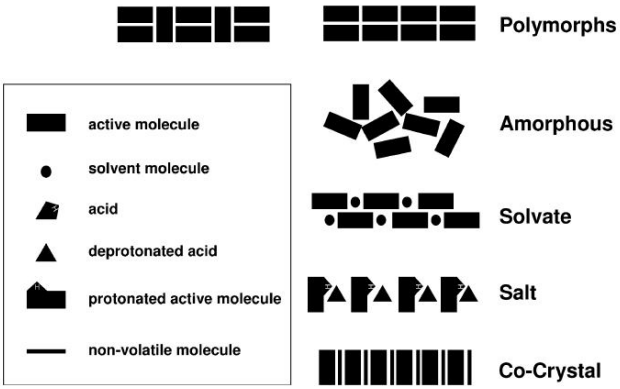

Fig 1. Schematic depiction of various types of solid forms.

CO-CRYSTAL VERSUS SOLVATES

The main difference between solvates and co-crystals is the physical state of the isolated pure components: if one component is a liquid at room temperature, the crystals are designated as solvates; if both components are solids at room temperature, the crystals are designated as co-crystals.

SALT VERSUS CO-CRYSTAL FORMATION

Co-crystal and salts may sometimes be confused. The understanding of the fundamental difference between a salt formation and a co-crystal is very important to both pre-formulation activities and chemical/pharmaceutical development aspects. Indeed, salts and co-crystals can be considered as opposite ends of multi-component structures (Stahly, 2007; Childs, 2007). Salt are often chosen instead of the free acid or base as these can improve crystallinity, solubility and stability of a pharmaceutical compound. Co-crystals are an alternative to salts when these do not have the appropriate solid state properties or cannot be formed due to the absence of ionizable sites in the API. Salt formation is an acid–base reaction between the API and an acidic or basic substance. The widespread use of salt formation is evidenced by the large number of marketed crystalline salts of APIs (Stahl, 2002; Serajuddin, 2007). Salt formation is a three component system having an acid (A), a base (B) and one or more solvents. A salt is formed by transfer of a proton (H^+) from an acid (A) to base (B).

$$A\text{-}H + B \rightarrow (A^-)\ (B^+\text{-}\ H)$$

Proton transfer is thought to mainly depend on the pK_a values of the components. The general rules for the packing of hydrogen bonded molecules in crystals were developed (Etter, 1982, 1990 and 1991). When there is no such transfer and the

components are instead present in the crystal as neutral entities, the product is generally defined as a co-crystal. In other words, a co-crystal is an A-B composite in which no proton transfer occurred. A thermodynamic picture (see Figure 3) of the nucleation phenomenon reveals interplay between the volume and surface terms in nucleation initiation. Volume term-favouring aggregation is an exothermic process that leads to a reduction in Gibbs free energy throughout the system. On the other hand, surface term allows the dissolution of molecular aggregates, which would otherwise be nucleating, by utilising energy. r* is the critical radius of molecular aggregate at which nuclei spontaneously grow. Formation of nuclei is a compromise between volume and surface term. Volume term favours aggregation whereas surface term allows dissolution. Nuclei result when there is high volume–surface ratio. Below r*, aggregates dissolve whereas above r* nuclei form macroscopic crystals Figure 2.

The diffusion-controlled formation of a liquid-like cluster of solute molecules; and/or the organisation of clusters into an ordered crystalline structure Figure 3.

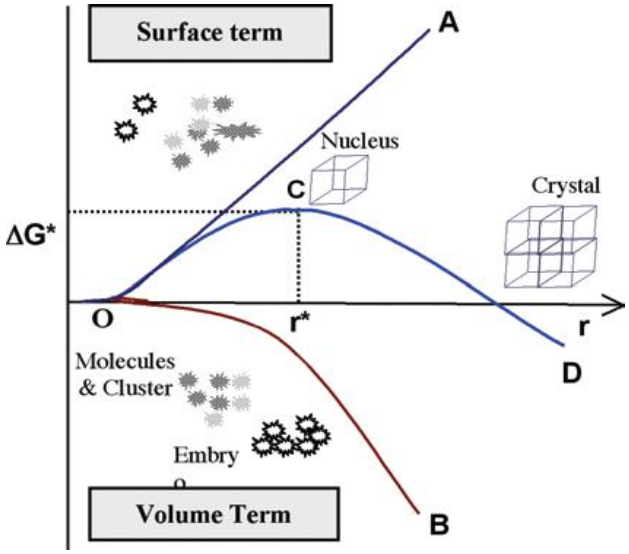

Fig 2. Thermodynamic Relationship between Activation Energy for Nucleation and Mean Radius of Molecular Aggregate.

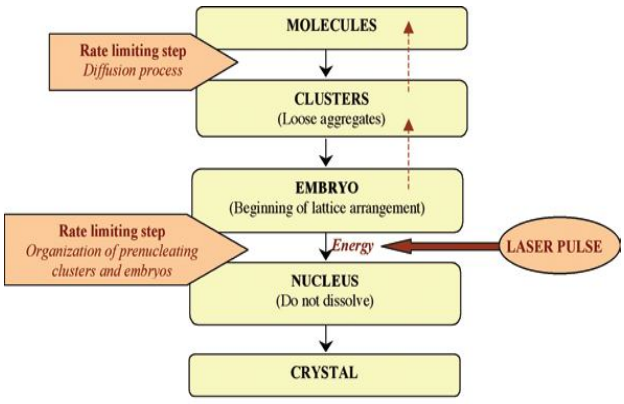

Fig 3. Course of Crystallization and its Rate-limiting Steps.

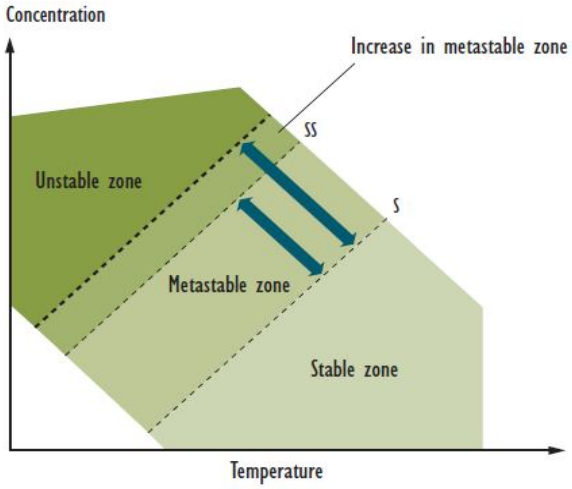

Fig 4. Concentration of Solute during Crystallization.

Supersaturation is the basic driving force for crystallisation and is defined as the concentration of the solute in excess of saturated concentration under given conditions of temperature. It is composed of two zones, the metastable and unstable zones Figure 4. The two zones are defined so that the metastable region shows crystals growing without nucleating, whereas in the unstable region crystals appear after nucleation.

The formation of a salt or co-crystal can be predicted from pKa value of acid (A) and a base (B). Salt formation generally requires a difference of about 2.7 pKa units between the conjugate base and the conjugate acid (A) i.e. [pKa (base) - pKa (acid) ≥ 2.7]. For example, succinic acid having pKa 4.2 form co-crystal with urea base (pKa 0.1) while succinic acid form salt with L-lysine base having pKa 9.5. Generally base pKa values are not sufficiently high to allow proton transfer when co-crystal is formed (Whitesides, 2006).

Cocrystal Solubility

Cocrystal solubility is dependent on cocrystal component concentration, solution complexation, and ionization when one or more components are ionizable. Mathematical models have been developed that describe the solubility of binary cocrystals with nonionizable components based on the equilibria between cocrystal and cocrystal components in solution (Nehm, Rodríguez-Spong *et al.*, 2006).

Bioavailability

If cocrystals are going to be a viable alternative for solid state forms of a drug, bioavailability studies need to be performed. Two manuscripts have been recently published that report the first bioavailability studies using cocrystals.

CHARACTERIZATION OF CO-CRYSTALS

Characterization of co-crystals involves both structure (infrared spectroscopy, single crystal x-ray crystallography and powder x-ray diffraction) (Callear, 2008; Wenger, 2008; Basavoju S, 2008) and physical properties (e.g. melting point apparatus,

differential scanning calorimetry, thermogravimetric analysis) (Basavoju S, 2008; Lu J, 2009). The analytical potential of NIR spectroscopy for co-crystal screening using Raman spectroscopy as a comparative method has been reported (Allesø M, 2008). A compound-sparing, automated and green differential scanning calorimetric method was developed for rapid co-crystal screening which demonstrated the formation of carbamazepine - nicotinamide co-crystals (Lu E, 2008). Co-crystals of a phosphodiesterase-IV inhibitor with L-tartaric acid were characterized (Variankaval *et al.*, 2006). Co-crystals of (−)-gossypol with a C1-8 carboxylic acid or C1-8 sulfonic acid which are useful as inhibitors of Bcl-2 family proteins and use of co-crystals of (−)-gossypol with a C1-8 carboxylic acid or C1-8 sulfonic acid for inducing apoptosis in cells and for sensitizing cells to the induction of apoptotic cell death were characterized ((e.g. (-)-Gossypol- acetic acid co-crystals) (Wang S, United States Patent 7432300).

Plots of pH versus solubility were employed to compare the solubility of molecular salts and co-crystals (Cooke C., 2008). Mathematical model was developed that describes the solubility of co-crystals by taking into consideration the equilibria between co-crystal, co-crystal components, and solution complexes and was applied to the phase diagrams of carbamazepine/nicotinamide co-crystal in organic solvents. The dependence of co-crystal solubility on solubility product and complexation constants provided a powerful approach to design co-crystal screening methods and to formulate solutions with co-crystal components where crystallization does not occurred (Nehm S., 2006). A method was developed to estimate the co-crystal solubility in pure solvent and co-crystal solubility was found to be directly proportional to the solubility of constituent reactants for carbamazepine, caffeine, and theophylline co-crystals (Good D., 2009). The phase transformation of API to co-crystal has been shown to depend on solution and co-crystal chemistry where non-stoichiometric concentrations of co-crystal reactants lead to thermodynamically favorable conditions for co-crystallization.A new approach to model co-crystal phase diagrams was recently reported and its application to an active pharmaceutical ingredient and glutaric acid co-crystal demonstrated good agreement between calculated and experimental data (Ainouz A., 2009). The scientists provided the foundation to experimentally assess the thermodynamic stability of a co-crystal with respect to its component forms using data for the carbamazepine–nicotinamide system (Schartman R., 2009). Co-crystal formation should generally be predictable by comparing the relative stability of the most stable co-crystal and its pure components found on the computed crystal energy landscapes. The thermodynamically favored structure prediction of the co-crystals of p-aminobenzoic acid with 2,2'-bipyridine, based only on the atomic connectivity of the component molecules and assumed stiochiometry was reported (Karamertzanis P., 2008).

The most stable solid form of tiotropium fumarate i.e. a new salt-co-crystal of tiotropium fumarate with fumaric acid structure consisted of matched cations and anions (a salt) together with a nonionized free acid moiety as the co-former (co-crystal), and is unique amongst the large number of tiotropium salts that have been prepared and characterized. The stoichiometry cation/anion/co-former of 2:1:1 corresponded to a simple polymorph of the 1:1 salt, and its identity as a co-crystal has been established by single-crystal X-ray diffraction with some corroborating evidence from the Raman and infrared spectra. A detailed investigation of the bonding and geometry of the three crystalline forms of the fumarate indicated that the hydrogen bonding motifs are very similar, and that conformational differences arising from the packing of the two thiophene rings into the crystal structure is probably important in determining their relative stabilities. A comparison with the structures of other tiotropium salts indicated a correlation of the dihedral angle between the two tiotropium thiophene rings with the stability of the crystal forms (Pop M., 2009). Curcumin, the main component of the spice turmeric, has been successfully used as a therapy to treat human multiple myeloma (Schultz D., 2008). Also has shown to possess anti-inflammatory and anti-cancer activities . However, curcumin has extremely poor water solubility and bioavailability. A series of pharmaceutically acceptable co-crystal formers are under investigation to screen for co-crystal formation of curcumin (Handler., 2007) .

Pharmaceutical co-crystals as intellectual property

Compared to other classes of solid forms, co-crystals possessed particular scientific and regulatory advantages, and alongside these advantages were intellectual property issues which give co-crystals with unique opportunities and challenges. Researchers reported **t**he importance regarding patents on pharmaceutical co-crystals to the pharmaceutical industry (Trask, 2007). The value of co-crystals to the pharmaceutical industry should become clearer, mainly with respect to several relevant legal and regulatory issues, as products containing co-crystal technology come out from pharmaceutical development pipelines onto the market.

APPLICATIONS OF CO-CRYSTALS

Compared to other solid-state modification techniques employed by pharmaceutical industry, co-crystal formation appears to be an advantageous alternative for drug discovery (e.g. new molecule synthesis, nutraceutical co-crystals), drug delivery (solubility, bioavailability) and chiral resolution. Experts are of the opinion that pharmaceutical intellectual property landscape may benefit through co-crystallization (Trask, 2007).

CONCLUSIONS AND PERSPECTIVES

Pharmaceuticals having a prominent role in the healthcare of the future and pre-formulation activities need to utilize innovations to respond to the challenges of new discoveries. The newer crystallization techniques provide effective means to discover alternate solid-state forms in complex organic molecules like drugs. These techniques are comprehensive, they are accompanied by enhanced crystallisation rates and they potentially bypass the limitations of additive addition. Ascertaining the

metastable forms can prove to be of immense help for those molecules that fail to arrive at the market because of their insoluble temperament. Represent an advantageous class in the context of pharmaceuticals.co-crystal form represent a new type of material for pharmaceutical development and are relatively new to pharmaceutical industry and pharmaceutical co-crystals have given a new direction to deal with problems of poorly soluble drugs and much more useful in pharmaceutical products than solvates or hydrates. Relevance in API formulation includes the ability to fine-tune physical properties, characterization of API, identify and develop new, proprietary forms of prescribed drugs and the opportunity to generate intellectual property. 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. Judicious use of these innovative technologies therefore, can help pre-formulation scientists to 'unveil' the hidden fortunes present as alternate solid forms. The portfolio of solid forms of pharmaceutical molecules is nowadays very wide and somehow difficult to overlook. A further increase in number of new co-crystals, or multicomponent compounds generally, and their application in solid drug formulations are expected in future.

Conflict of Interest: Veerendra K Nanjwade is a Research Scholar in the Pharmaceutics Department of KLE University College of Pharmacy, Belgaum. But he declares no conflict of interest regarding the manuscript. The other authors declare no conflict of interest.

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