Review Article

Co-crystal: A pharmaceutical technique to improve physical characteristics of Active Pharmaceutical Ingredient

Reetu Yadav[1]*, Ashutosh Kumar Yadav[1], Anita Singh[2]

[1]*K.R. Mangalam University, Sohna Road, Gurugram, Haryana 122103 India*

[2]*Sunderdeep Pharmacy College, NH-24, Delhi-Hapur Road, Dasna, Ghaziabad-201015 (U.P) India*

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Abstract

Co-crystal is defined as a material which contains two or more discrete molecular entities in the crystal structure. Co-crystals of many compounds are known for years in solid state chemistry. Pharmaceutical co-crystals are important because they can improve many properties of the parent API like solubility, dissolution rate, stability, crystallinity and many more. Biopharmaceutics Classification System (BCS) of drugs classifies drugs into four major categories based on their solubility and permeability behavior. BCS Class II and Class IV drugs suffer from poor aqueous solubility. Co-crystallization enhances solubility of BCS class II and class IV drug, in addition to BCS of drugs. The aim of this review is to present an extensive overview of the co-crystallization methods, focusing in the specificities of each technique, its advantages and disadvantages.

Keywords: Cocrystal, solubility enhancement, co-crystallization method

Introduction

Co-crystal is defined as a material which contains two or more discrete molecular entities in the crystal structure. Co-crystals of many compounds are known for years in solid state chemistry. However, it is only recently that pharmaceutical cocrystals have generated much commercial and academic interest. Pharmaceutical cocrystals are important because they can improve many properties of the parent API like solubility, dissolution rate, stability, crystallinity and many more (Almarsson and Zaworotko, 2004). Biopharmaceutics Classification System (BCS) of drugs classifies drugs into four major categories based on their solubility and permeability behavior. BCS Class II and Class IV drugs suffer from poor aqueous solubility. Poor aqueous solubility of hydrophobic drugs can result in poor absorption, low bioavailability and poses challenges for drug development process (Desiraju, 2003a). Enhancing bioavailability of poorly water-soluble BCS class II and BCS class IV drugs therefore becomes necessary to improve drug's efficacy. Co-crystallization enhances solubility of BCS class II and class IV drug. In addition to BCS of drugs, Developability Classification System (DCS) of drugs also plays a significant role in determining the development of pharmaceutical formulations, especially the oral formulations based on its solubility in biorelevant media such as FaSSIF (Fast State Simulated Intestinal Fluid) and FeSSIF (Fed State Simulated Intestinal Fluid) rather than its solubility in buffers (Dunitz, 2003b; Jain and Patel, 2015; Vadher et al., 2009). Very few reports are available in the literature where researchers have determined the dissolution rate of cocrystals of poorly water-soluble drugs in biorelevant media. The studies illustrate that cocrystals exhibited enhanced dissolution rate in biorelevant media and buffer as well indicating that the DCS serves as a highly relevant tool in determining develop ability of cocrystals of poorly water-soluble APIs. Enhancing aqueous solubility of poorly water-soluble drugs without compromising on stability is one of the major challenges faced by the pharmaceutical industries during drug discovery and development processes (Steed, 2013). Crystal Engineering is a tool which can be used to tailor the physicochemical properties of Active Pharmaceutical Ingredients (APIs) such as melting point, dissolution rate, aqueous solubility, refractive index, surface activity, habit, density, electrostatic, mechanical and optical properties. Cocrystallization is one of

Address for Corresponding Author:
Reetu Yadav
K.R. Mangalam University,
Sohna Road, Gurugram, Haryana 122103 India
Email: rituarp@gmail.com

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the crystal engineering approaches adopted to prepare multicomponent pharmaceutical crystals to enhance the dissolution rates of poorly water-soluble APIs without affecting their intrinsic properties (Kumar et al., 2013)`

Co-crystal development

Pharmaceutical co crystals can be defined as crystalline materials comprised of an Active Pharmaceutical Ingredient (API) and one or more unique co crystal formers, which are solids at room temperature. Co crystals can be constructed through several types of interaction, including hydrogen bonding and vander Waals forces. Like hydrates, co-crystals are nonionic supra molecular complexes; but like salts, co-crystals involve complexation with substances of greater potential toxicity than water (Mathur et al., 2011). Solvates and hydrates of the APIs are not considered to be co crystals by this definition. However, co crystals may include one or more solvent/water molecules in the crystal lattice (Matthew et al., 2006).

Characterization methods

Co crystals need to be analyzed by using different analytical methods. The Fourier transform infrared spectroscopy (IR), Nuclear magnetic resonance spectroscopy (NMR), Powder X-ray diffraction (PXRD), Single crystal X-ray diffraction (SXRD), Differential scanning calorimeter (DSC) and Thermo Gravimetric Analyzer (TGA) methods are routinely being used for characterizing co crystals.

Powder X-ray diffraction (PXRD)

Powder X-ray diffraction (XRD) is a most reliable and non-destructive technique that reveals detailed information about the crystallographic nature of the materials.

Single crystal X-ray diffraction (SXRD)

Single-crystal X-ray Diffraction is a non-destructive analytical technique which provides detailed information about the internal lattice of crystalline substances, including unit cell dimensions, bond-lengths, bond-angles, and details of site-ordering. Directly related is single-crystal refinement, where the data generated from the X-ray analysis is interpreted and refined to obtain the crystal structure.

Thermal analysis techniques

Thermal analysis generally refers to any method involving heating the sample and measuring the change in some physical property. The most important thermal methods for the study of solid state Chemistry are Differential scanning calorimetry and thermogravemetric analysis (Nair et al., 2007; Byrn et al., 1990; Harry et al., 1999; Andrew, 2007; Yadav et al., 2009; Giron, 1995).

Differential scanning calorimetry (DSC)

Differential Scanning Calorimetry (DSC) is one of many types of thermal analysis techniques useful for characterizing pharmaceutical solids. Materials of different quality and materials prepared differently are useful to characterize the crystalline properties of a material. Characteristic Differential Scanning Calorimetry measurements include the glass-transition temperature, melting and crystallization temperatures, specific heat (Cp) and the heat of transition (ΔH)(Malamatari et al., 2017; Chan et al., 2013; Musumeci et al., 2011; Shan and Zaworotko, 2008).

Thermogravimetric analysis (TGA)

Thermogravimetric analysis measures the change in the mass of sample as the temperature is changed. Weight loss occurs due to loss of volatile materials that exist in the sample in its normal state or are created by the application of heat (e.g., reaction products). TGA has the additional advantage, over other techniques of water content measurement i.e. of the ability to distinguish between bound water and free water, which can help identify water evolving from the sample. In many instances TGA greatly simplifies the interpretation of complex DSC curves (Yamashita et al., 2013).

Methods of preparation of Co-Crystals

Design strategies for co-crystal formation are still being researched and the mechanism of formation is far from being understood. Co-crystals can be prepared by solvent and solid based methods. The solvent-based methods involve slurry conversion solvent evaporation, cooling crystallization and precipitation. The solid based methods involve net grinding; solvent-assisted grinding and sonication (applied to either to wet or dry solid mixtures) 80° to 85° (Childs et al., 2008; Thipparaboina, 2016; Aakeröy et al., 2003; Zaworotko, 2005).

Solution co-crystallization

For solution co-crystallization, the two components must have similar solubility; otherwise the least soluble component will precipitate out exclusively. However similar solubility alone will not guarantee success. It has been suggested that it may be useful to consider polymorphic compounds, which exist in more than one crystalline form as co-crystallising components. If a molecular compound exists in several polymorphic forms it has demonstrated a structural flexibility and is not locked into a single type of crystalline lattice or packing mode. Thus, the chance of bringing such a molecule into a different packing arrangement in coexistence with another molecule is increased. Clearly polymorphism alone does not guarantee the functionality of a compound to act as a co-crystallising agent, whilst the ability of a molecule to participate in intermolecular interactions obviously plays a

critical role (Blagden et al., 2007). Small-scale preparation has been described. Scale-up crystallization was performed in a 500 ml water-jacketed glass crystallization vessel. Temperature was maintained by a circulating water bath. A reflux column, digital thermometer, and overhead stirrer with a glass shaft and Teflon blade were attached to vessel ports. The drug and co-crystal former were added to a reaction vessel. The solids were dissolved in ethanol/methanol mixture and heated to 70° for 1 h under reflux. Temperature was decreased in 10° increments to induce precipitation in a stirred, unseeded system. Observe the appearance of the co-crystal. Literate to enhance solids recovery decrease the further temperature.

Grinding

When preparing co-crystals, the product obtained from grinding is generally consistent with that obtained from solution. This may indicate that hydrogen-bond connectivity patterns are not idiosyncratic or determined by non-specific and unmanageable solvent effects or crystallization conditions. Nevertheless there are exceptions. Whilst many co-crystal materials can be prepared from both solution growth and solid-state grinding, some can only be obtained by solid-state grinding. An example is that in the co-crystallisation of 2, 4, 6 trinitrobenzoic acid and indole-3-acetic acid, different crystal forms were obtained from solution compared with grinding. Failure to form co-crystals by grinding may be due to an inability to generate suitable co-crystal arrangements rather than due to the stability of the initial phases. When co-crystal formation has been successful from solution, but not from grinding, solvent inclusion in stabilizing the supramolecular structure may be a factor. Although co-crystal formation by solid-state grinding has been established for some time and a late 19 century report is often cited as the earliest reference to such a procedure, the recent technique of adding small amounts of solvent during the grinding process has been shown to enhance the kinetics and facilitate co-crystal formation and as lead to increased interest of solid-state grinding as a method for co-crystal preparation (Blagden et al., 2007).

Slurry conversion

Slurry conversion experiments were conducted in different organic solvents and water. Solvent was added to the co-crystal and the resulting suspension was stirred at room temperature for some days. After some days, the solvent was decanted and the solid material was dried under a flow of nitrogen for 5 min. The remaining solids were then characterized using PXRD.

Antisolvent addition

This is one of the methods for precipitation or recrystalization of the co-crystal former and active pharmaceutical ingredient. Solvents include buffers (pH) and organic solvents. For example preparation of co-crystals of aceclofenac using chitosan, in which chitosan solution was prepared by soaking chitosan in glacial acetic acid. A weighed amount of the drug was dispersed in chitosan solution by using high dispersion homogenizer. This dispersion was added to distilled water or sodium citrate solution to precipitate chitosan on drug (Mutalik et al., 2008).

Effective cocrystal preparation methods in use today can be classified as:

(1) Solid (grinding, solvent-assisted grinding, sonication) and (2) Solvent-based (slurring, solvent evaporation, crystallization from solution or active cocrystallization and antisolvent addition).

For the solvent-based methods, the selection of the solvent is crucial, since its potential change will alter the intermolecular interactions and potentially lead to better cocrystallization results. Other methods may also have constraints, such as:

- Thermal methods that require melting need high temperatures, which can affect the integrity of heat-sensitive compounds.
- Mechanical methods, such as grinding, require energy consumption and can produce amorphous materials, limiting their effectiveness if a suitable solvent is not used.
- Methods based on precipitation from solution require continuous and precise control of the supersaturation level of the components' concentration and necessitate the creation of phase diagrams, while the use of a solvent is not environmentally friendly.

Kuroda et al. (2002) suggest that shearing and molecular diffusion during grinding can generate a different additive structure, while vapor diffusion has also been proposed as a mass transport mechanism during the grinding of the solid state (Rastogi et al., 1963). In solvent-based methods, it is necessary to control several variables to select the conditions for the generation of the nuclei and the cocrystal development, in addition to the selection of the solvent. For instance, cocrystal nucleation depends on parameters such as concentration, temperature, cooling rate and rate of evaporation. The most common method of industrial production (on a large scale) of cocrystals is the cocrystallization of an API by a supersaturated solution in the presence of a coformer. In most cases, about 40% supersaturation is achieved through the slow cooling of an undersaturated mixture until the dissolution limit is reached. Additionally, solution mediated phase transitions (SMPT) can be induced by manipulating the amount of the coformer (reaction cocrystallization). The addition of a certain amount of one of the components of the cocrystal system has been used as a retreatment process in cases

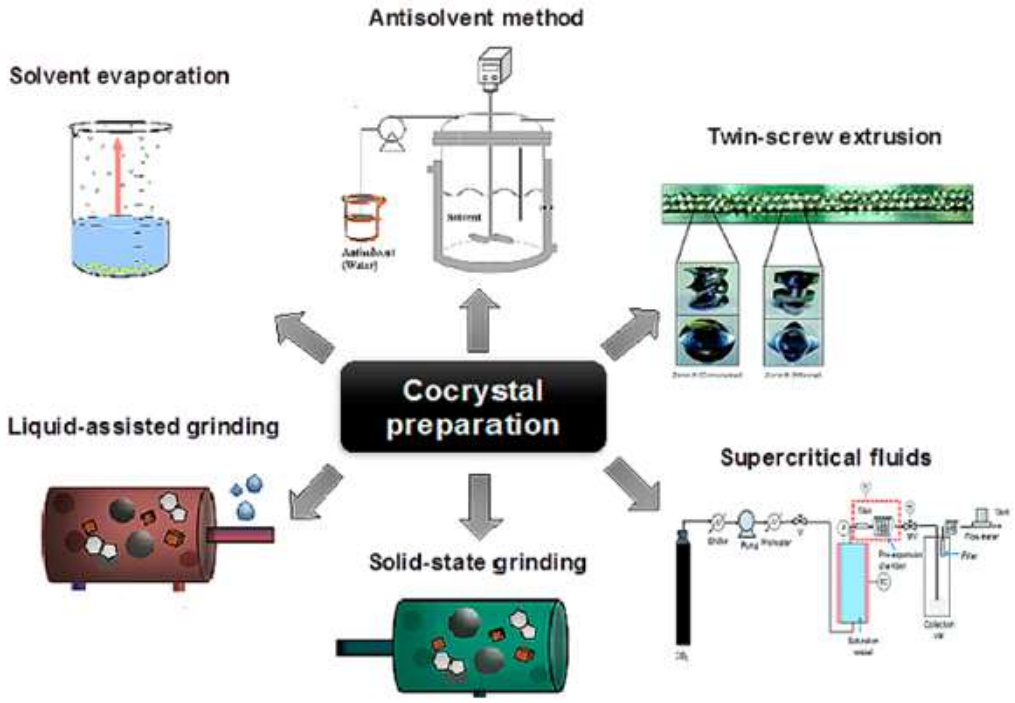

Figure 1. Schematic representation of method applied in co-crystal formulation

where the cocrystal phase was polluted by another crystalline phase (coformer or API) Gagnière et al., 2011). The key to the composition of high-purity cocrystals is the understanding of the binary or ternary phase diagram for the equilibrium, which includes the solvent (if there is one) and the two components. The binary phase diagram of the two cocrystal components (the drug and the coformer, in the case of pharmaceutical cocrystals) shows that the eutectic points between each phase, and thus the existence and the number of the phases of the cocrystal (Blagden et al., 2008; Chiarella et al., 2007).

Chadwick et al. (2007) studied cocrystal formation at room temperature, and stressed the importance of the intermediate metastable eutectic liquid phase, which facilitates the transport of intramolecular mass leading to cocrystallization. Based on these studies, they concluded that systems with eutectic temperatures close to ambient temperature are prone to the formation of cocrystals through dry grinding, while in those with eutectic temperatures above the ambient temperature, the addition of solvent helps cocrystal formation. Shan et al. (2002) further explained that grinding in the presence of a few drops of solvent results in a system with increased degrees of freedom. The increase in molecular collision facilitates the initial formation of cocrystal nuclei. A quick description of the methods applied in pharmaceutical cocrystal formation follows, apart from the slow cooling of an undersaturated solution and the solution mediated phase transitions (reaction cocrystallization) described above (Figure 1)(Karagianni et al., 2018).

Solvent evaporation technique

This is the most commonly used technique for generating cocrystals. The materials (API and coformer) are dissolved in a common solvent with a suitable stoichiometric ratio and completely evaporate (Weyna et al., 2009). During evaporation, the solution of the molecules undergoes changes, with the creation of hydrogen bonds between different functional groups, thus producing a thermodynamically favoured product. The selection of the solvent plays an important role in solubility. If the solubility of the two components is not similar, then the component with the lower solubility will precipitate. Preparation of cocrystals by solvent evaporation is a small-scale technique that does not require complex equipment, and results in cocrystals of high quality and purity. However, the use of large amounts of solvent and its limited scalability are two disadvantages to this technique (Childs, 2004).

Solid-state grinding technique or neat grinding

This is a cocrystallization method without a solvent. The solid materials that will result in the cocrystal are admixed in appropriate stoichiometric amounts, pressed and crushed together with a mortar and pestle, or a ball mill or vibrator mill. The common grinding duration ranges from 30 to 60 min. With this method, numerous cocrystals can be prepared, and any failure is generally due to the use of inappropriate settings.

Reducing the particle size increases the specific surface area of interaction between the materials for the development of intermolecular bonds. This offers the advantage of increased selectivity compared to cocrystallization through dissolution. It is simple, and allows quick preparation of the desired cocrystal. Experiments on mixing cocrystals with other components that can also form cocrystals with the API have been carried out. In the latter case, the coformer is replaced, and this can be used either to assess the stability of a cocrystal in the presence of other excipients or to disclose alternative modifications of the cocrystals. Modifications that don't necessarily take place in the process of dissolution, e.g., caffeine-trifluoroacetic acid cocrystal, were initially only obtained by grinding (Trask et al., 2005). That is to say that it has also been used as a method of clarifying hydrogen bond preference.

Mechanochemistry (i.e., solid-state grinding) was used for the patent of the pterostilbene-caffeine cocrystal (Schultheiss et al., 2011).

Liquid-assisted grinding, or solvent-drop grinding

This is a modification of neat grinding by adding a small amount of solvent during the grinding process, and has been used to enhance supramolecular selectivity, both polymorphic and stoichiometric, in crystalline systems. It includes mixing the two components and adding a very small amount of solvent (~a few tenths of an equivalent of solvent per mole of the component). The effect of the solvent can be described as catalytic, as its small amount is not part of the final product. Its advantages lie in its increased performance, in the ability to control the production of polymorphs, and in the improved crystallinity of the product, while a large number of coformers are suitable for the cocrystallization. This method enhances the cocrystallization rate, as some cocrystals showed poor performance in cocrystal formation following neat grinding for a considerable amount of time (Trask et al., 2004). This method can be used to prepare high-purity cocrystals with a significant reduction in the preparation time. It also allows the synthesis of selective polymorphic forms of cocrystals. For instance, in caffeine-glutaric acid (1:1) cocrystals, neat grinding resulted mainly (not always) in form I, while liquid-assisted grinding to pure form I with less polar solvent (e.g., cyclohexane or hexane) and to pure form II with more polar solvent (e.g., water or acetonitrile) (Trask et al., 2004).

This allows interconversion between crystalline forms of polymorphic organic components, depending on the polarity of the solvent. Limitations of liquid-assisting grinding include the fact that it is a small-scale technique, requires high energy consumption, and has a low performance in terms of product purity. Liquid-assisted grinding was used for the patent of pterostilbene-carbamazepine cocrystals (Schultheiss et al., 2010).

Slurring technique

This is a simple process, whereby crystallization solvent is added (Takata et al., 2008). The solid API dissolves in the solvent, forming a solution into which the coformer is added, after which the resulting suspension is stirred, filtered and dried. Slurring was used for the patent of celecoxib-venlafaxine cocrystals (Plata et al., 2012). This multi-drug cocrystal combines the therapeutic properties of celecoxib (which has anti-inflammatory properties for patients with chronic musculoskeletal inflammatory diseases) and venlafaxine (with an antidepressant effect).

Antisolvent cocrystallization

A solvent in which the compound is less soluble is often added to the solution, favoring the precipitation of the solids. The resulting suspension is filtered, and the collected solid can be characterized by XRPD. Disadvantages of this method are its lower performance compared to grinding that uses a solvent, as well as the large volume of solvent used. Antisolvent crystallization has been reported for the production of carbamazepine-saccharin and indomethacin-saccharin cocrystals (Wang et al., 2013; Chun et al., 2013). In both studies, the construction of phase solubility diagrams was an integral part of the methodology for identifying the optimal conditions (e.g., ratio of solvent to anti-solvent) for the formation of cocrystals.

Use of supercritical fluids

Supercritical fluid (SCF) is a very good solvent, and has the unique ability to diffuse through solids like a gas and dissolve materials like a liquid (gas flow properties and dissolving liquid properties); thus, it can replace organic solvents. CO2 is the most frequently used supercritical fluid for cocrystallization as solvent, as anti-solvent and as atomized anti-solvent (Padrela, 2009). A detailed review of the preparation of pharmaceutical cocrystals through sustainable process using supercritical carbon dioxide has been provided by Pando et al. (2016).

Cocrystallization with supercritical solvent (CSS)

The active substance and the coformers are dissolved in the supercritical CO_2 (sc-CO*2*) inside a stainless-steel vessel, and depressurization then leads to the loss of dissolving dominance of sc-CO2, to supersaturation and eventually to the formation of cocrystals. The application of CSS requires sufficient (ideally equal) solubility of the pure components in sc-CO2. Its main disadvantage is its low performance in pure products.

Supercritical antisolvent (SAS)

If a substance is not soluble in sc-CO2, the sc-CO2 can be used as an anti-solvent for a solution of cocrystal components (coformer and API) in an organic solvent. Therefore, the

active substance and the coformers dissolve into an organic solvent (primary solvent). This is followed by its dropwise mixing with the sc-CO2 by passing the organic solution through a nozzle. The sc-CO2 dissolves quickly in the droplets of the organic solution, reduces the dissolving power of the solvent and simultaneously extracts it, causing saturation and supersaturation, during which cocrystallization nuclei are formed and the precipitation of cocrystals by the anti-solvent effect of sc-CO2 takes place. This technique requires complete miscibility of the organic solvent with the sc-CO2 and lower solubility for the solute in the mixture.

Then, the organic solvent is removed, and a product without solvent is obtained. Itraconazole (antifungal drug of poor bioavailability) and succinic acid cocrystals preparation, with sc CO2 as an antisolvent, is an example of such, while the same method was used for the patent of the carbamazepine-aspirin cocrystal (Ober and Gupta, 2012; Mazen and Townend, 2008).

Atomized anti-solvent (AAS)

In the AAS technique, the sc-CO2 enhances the atomization of the organic solution, producing particles by two different mechanisms: antisolvent crystallization and spray-drying crystallization. The solution containing the API and coformer is pumped through a coaxial nozzle, where it mixes with the sc-CO2 or N2 in the mixing chamber prior to its depressurization into the precipitator vessel (for SAS technique, the precipitator is filled with CO2 at high pressure, whereas in the AAS technique, it is at ambient pressure). Pure indomethacin–saccharin cocrystals have been produced by the AAS technique (Shekhar et al., 2017).

Sonocrystallization

Ultrasound, apart from its wide application in various fields of medicine (e.g., as a diagnostic method) and cosmetology, offers promising prospects in the generation of nuclei during the process of crystallization of drugs. For example, it has been used for the formation of pharmaceutical microparticles sized 2–6 um, primarily intended for inhalation (Shekhar et al., 2017). The generation of such particles through mechanical methods causes problems of physicochemical stability, performance, and product modification, attempts to improve all of which are being made through the use of the escalating power of ultrasound.

When the ultrasound waves pass through the inner part of the liquid solution with alternating cycles of high pressure (compression)–low pressure (thinning), they create air bubbles or voids in the liquid. The volume of the air bubbles increases due to the absorption of the supplied energy of the ultrasound. However, when supersaturation occurs and they cannot absorb any more energy, during a high-pressure cycle, they collapse in the liquid violently and the temperature increases due to the release of the energy of the bubbles. This collapse is referred to as cavitation. The content of the air bubbles is quickly compressed. This results in the promotion of crystallization and precipitation, since homogeneous mixing of API and coformer has already been achieved. At the moment of total collapse, the vapor's temperature can reach ~50,000 K and its pressure ~200 atm. The whole energy supply to the liquid is continuously monitored through the ultrasonic monitor. Thus, API and coformer are added in the appropriate solvent in similar stoichiometric proportions, and their solution is generated, which is subsequently sonicated. The ultrasonic waves are of high intensity, ~20 KHz, and promote the formation of crystallization nuclei.

Cocrystal formation under sonication depends on several parameters, such as the solvent, the time of sonication, the saturation levels of the APIs and the coformer. The sonocrystallization technique was used for the patent of the hydrochloride fluoxetine cocrystal with benzoic acid in acetonitrile (Childs, 2011).

Intermediate phase or form modifications

Generating cocrystals requires a process of modification of the phases or forms of the API and the coformers (e.g., melt, solution, polymorphic transition, etc.) to achieve successful cocrystallization. The required modification may pass through consecutive intermediate stages, not all of which are always easily identifiable, because the transitions are very fast, no matter which process is used (e.g., grinding, solvent grinding, melt cooling, moisture sorption).

The intermediate forms, such as hydrates, amorphous form or metastable polymorphic form, act as unstable intermediates in the cocrystallization nucleus (Jayashankar, 2006). However, in this method a thorough examination of the thermodynamic properties of the compounds is necessary.

Intermediate phases or forms that have been identified have, until recently, been elucidated by interruption of the process, e.g., stopping the grinding and testing the product for new solid forms (amorphous, coamorphous, polymorphs, cocrystals, salts). These data have not always been reliable as a result of the possible moisture sorption and recrystallization that can occur during testing, since the examination has not taken place in real-time (in situ).

A contemporary technique for direct and real-time (in situ) monitoring of transformations during the process has been carried out using X-ray diffraction. The first application through intermediate amorphous phase was in a carbamazepine-saccharin mixture. The difference between neat and liquid-assisted grinding was found to be significant, as the latter creates cocrystals very quickly (in 2 min) compared to neat grinding, where amorphous intermediate phases could be observed (Halasz, et al.,

2013). This method provided, for the first time, a rapid in situ process of cocrystallization, as well as the study of several intermediate phases that had not previously been observed. Intermediate form modifications were used for the patent of generating choline cocrystals, which protect against diabetic complications and provide cardioprotection for non-diabetic patients, too (Kalofonos et al., 2017).

Spray drying

This method has been used recently for generating cocrystals (James, 2010). Solutions of disparately saturated systems lead to the formation of pure cocrystals, as opposed to the mixtures obtained after solvent evaporation. Thus, cocrystal formation can be monitored kinetically and/or mediated by the glassy state of the material.

Resonant Acoustic Mixing® (RAM)

This is a non-contact mixing technology that relies upon the application of a low-frequency acoustic field to facilitate mixing. This new technology has shown several advantages for numerous complexes and multiphase systems, while it reduces both mixing time and cost. Carbamazepine-nicotinamide cocrystals have been formed with this method by adding a solvent (20μL/100 mg of the cocrystal component) such as CH_3Cl, H_2O, DMF, DMSO, MeOH, and LabRAM was operated for two hours at 90% intensity with automatic tuning. This method can be used for cocrystal production at a large scale, and provides high-purity cocrystalline products (Am Ende et al., 2014).

Twin-screw extrusion (TSE)

Extrusion is the process of converting an unprocessed material or mixture of materials that have been ground or granulated into a product of uniform shape and density by pressing them through a die under controlled conditions (Breitenbach, 2002). During TSE, the mixture of the active substance, the thermoplastic polymer carrier, excipients, and other auxiliary agents (e.g., plasticizers, antioxidants), is heated in the extruder (Crowley et al., 2007). By the end of the process, a solid form (e.g., granules) is obtained from the output of the extruder. TSE was used for the patent of the L-malic acid and L-tartaric acid cocrystallization (Paradkar and Pagire, 2017). Medina et al. (2010) showed that the TSE technique can be used as an effective method for generating pharmaceutical cocrystals. Furthermore, the matrix-assisted cocrystallization (MAC) approach uses the TSE technique to produce cocrystals embedded in a formulation matrix. Equimolar amounts of API and coformer are mixed in solid form with a matrix material prior to the feeding in the extruder. The extruder is set at a temperature where only the matrix is liquid via either the formation of soft material or melt. Cocrystallization occurs during extrusion due to the mixing and grinding of the components in the pliable matrix. The cocrystal particles formed in this way are incorporated in the matrix, where they remain in a fluidized state until the exit from the extruder. In the MAC product, the material of the matrix plays a double role.

(1) During TSE it plays a role similar to that of a catalyst, for example, as a solvent. The use of a molten or pliable matrix promotes good mixing and reduces the excessive shear stress generated when solid materials are placed in the extruder. This reduction in the shear stress mitigates potential damage to the crystalline structure; and (2) The matrix acts a functional component of the formulated product in the finished product. Thus, the selection of the matrix material is very important for offering additional functionality to the formulated cocrystal, such as improved flowability, compressibility and release kinetics of the drug. The MAC method provides simultaneous production and formulation of the pharmaceutical cocrystal, giving high-quality cocrystals.

Conclusion

The main reason to the increase interest in cocrystals is the necessity to improve drugs properties. The improvement of solubility, dissolution rate and, consequently, bioavailability has been frequently reported, as well as the increase of stability and other properties that may have interest to drug development and drug storage. There are a large number of cocrystallization techniques, each one with a number of advantages and disadvantages. Solvent-based cocrystallization are the most widely used mainly because of procedures and apparatus simplicity, however they have several disadvantages mainly due to different solubilities of the cocrystal components and the use of hazardous solvents. Method selection is tremendously important and specific for each system. Solvent evaporation is applicable to systems without significant differences in solubilities and recommended as a screening procedure.

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