COCRYSTALS: A COMPLETE REVIEW ON CONVENTIONAL AND NOVEL METHODS OF ITS FORMATION AND ITS EVALUATION

BIJAY KUMAR YADAV¹, ATIF KHURSHEED², RATTAN DEEP SINGH²*

¹Department of School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India. ²Department of School of Bioengineering and Biosciences, Lovely Professional University, Phagwara, Punjab, India. Email: drrattandeep@gmail.com

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ABSTRACT

The active moiety with poor solubility is posing a challenge in drug development which may reduce the effectiveness in patients when administered orally. Cocrystal formation is one of the latest approaches for improving the various parameters of a drug molecule such as solubility, melting point, pharmacokinetic, pharmacodynamic, and bioavailability. Cocrystals are crystalline single state materials composed of two or more than two different molecular amalgams held together in a fixed stoichiometric ratio. There are various techniques used for the preparation of cocrystals such as solvent evaporation, grinding, and cooling crystallization. The quantitative and qualitative aspects of these cocrystals are evaluated using various validated instruments such as nuclear magnetic resonance, powder X-ray diffraction, and differential scanning calorimetry.

Keywords: Cocrystals, Coformers, Bioavailability, Crystallization, Grinding, Solubility.

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INTRODUCTION

Cocrystal concept of the supramolecular chemistry is gaining wide interest of researchers from pharmaceutical, chemical sciences, and regulatory agencies. Pharmaceutical cocrystal engineering has emerged as a new era in the field of medicine in developing a new moiety with improved solubility, dissolution, bioavailability, micrometric properties, and pharmacokinetic and pharmacodynamic properties of a drug. Cocrystals are crystalline and unagitated solid materials of two or more molecules held together within the same crystal lattice. However, pharmaceutical cocrystals are described as crystalline single state materials composed of two or more than two different molecular amalgams held together in a fixed stoichiometric ratio. The frequently accepted definition of pharmaceutical cocrystals, which emerged as a broad consensus opinion at the Indo-US meeting in 2011 and subsequently published in crystal growth and design is reproduced: “Cocrystals are solids crystalline single-phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts. Thus, it is a multiple component crystal modiﬁed by intermolecular interaction such as hydrogen bonding, van der Waals force, n-n interactions, and halogen bond between an active pharmaceutical ingredient (drug) and coformer [1]. This cocrystal possesses a neoteric property that is different from the parent drug molecule such as change in melting point, dissolution rate, micrometric properties, physicochemical properties, stability, permeability, and also, other various parameters of a drug moiety (4H). Hence, they can be easily patentable due to its novelty, non-obvious invention. Cocrystals are multicomponent crystals comprising salts, solvates, clathrates, inclusion crystals, and hydrates. In solvates, one component is liquid at room temperature whereas in cocrystals, both components are solid at room temperature [2]. The major steps involved for supramolecular synthon determination for the preparation of cocrystals are as:

1. Identification of important functional groups in the active pharmaceutical ingredients (API) or moiety.
2. Insertion of functional groups in a systemic way in the Cambridge structural database to select and identify most potent coformer.
3. Select an appropriate technique for the cocrystal synthesis.

Perform various crystallization screening processes [3].

In 1844, Friedrich Wohler first carried out isolation of a cocrystal between quinone and hydroquinone. The concept of supramolecular synths was first discovered by Gautam Desi Raju in 1955 which is considered as a key point in the study of crystal engineering for the synthesis of a new molecular entity. The US-FDA first approved a pharmaceutical ionic cocrystal drug in accordance with its cocrystal guidance paper for drug substance in 2012.

Examples of cocrystal drug in the market
1. Ernesto an antihypertensive drug (monosodium sacubitril+disodium valsartan+water) launched by Novartis for treatment of chronic heart failure in 2015
2. Lexapro (fluoxetine oxalate), an antidepressant drug (protonated escitalopram cations+water+oxalate dianion and deprotonated oxalic acid) approved in 2009
3. Ertugliflozin, an antidiabetic drug (5-oxo-proline+escitalopram)
4. Depakote (valproate sodium cocrystal in combination with valproic acid), most frequently used drug for the treatment of manic depression and seizure. It is one of the latest developments in the cocrystal formulation of a drug [4]. In general, the bond formation takes place between the adjacent moiety of a drug molecule leading to generation of new molecular compound with distinct properties [3h]
5. Bicalutamide and nicotinamide cocrystal-enhanced oral BA of 2.5-fold peak plasma concentration and 2.80-fold higher area under curve in rats
6. Hydrochlorothiazide-nicotinic acid cocrystal-enhanced solubility.

TECHNIQUES OF COCRystal FORMATION

With the advancement in drug development, various methods are being used for the preparation of multicomponent solid forms such as
as cocrystals, cosolvates, coamorphous, polymorphs, hydrates/salts, and eutectics. Solvent selection, API and coformers are the important parameters for such preparations. The various kinds of methods that are most commonly used are:

**Solid-based technique**

It generally includes solid phase grinding, melt extrusion, and melts crystallization. In this method, API and coformer are melted and mixed together, resulting in the cocrystal formation in a fixed stoichiometric ratio. It is basically not suitable for thermolabile moiety, but it is easy, scalable, and continuous process.

**Grinding method**

It is one of the mostly used techniques for the cocrystal formation from the last few years. It is basically of 2 types: (a) dry grinding method and (b) wet grinding method.

**Dry grinding method**

It is most widely and commonly used technique for cocrystal formation, in which API and coformers are mingled in a stoichiometric proportion using mortar and pestle. This method is simple, easy to perform, ecofriendly, and highly productive but is mechanical and time-consuming. Nowadays, planetary milling systems are also available in a laboratory scale [6]. The examples of cocrystals prepared by this method are carbamazepine-nicotine amide, piracetam-citric acid, and piracetam-tartaric acid [7]. The liquid-assisted grinding method had greater cocrystal formation efficiency than piracetam-citric acid cocrystal by grinding technique [8], acyclovir-succinic acid cocrystal [9].

**Hot melt extrusion method**

In this technique, API and coformers are transferred into a fixed controlled temperature system where they are melted and form cocrystals of new moiety [10]. This technique is not suitable for thermolabile drugs because both drug and coformer should be mixed in a molten state. In this method, API and coformer are mixed in their molten state to enhance their surface contact without the use of solvent (solution), for example, pyrazinamide cocrystals [11].

**Liquid-based technique**

This technique mainly includes: Solvent evaporation [12], solvent drop grinding [13], liquid-assisted grinding [14], solution crystallization [15], cooling crystallization [16], supercritical fluids [17], slurry method [18], antisolvent method [19], reaction crystallization method [20], ultrasound-assisted solution technique [21], supercritical fluid atomization techniques [22], and spray drying techniques [23].

**SLOW EVAPORATION OF SOLVENT RESULTS COCRystal FORMATION**

It is also known a solvent evaporation technique, in which a solution (solvent) is made to vaporize slowly. During the process of dissolution, the functional moiety in the API and coformer interchanges with each other to form new hydrogen bonds which is most widely used by many researchers, for example, glutaric acid cocrystals [24]. In this method, both API and coformers are dissolved with a continuous stirring in a boiling solvent until the final volume becomes small. This boiling solution is allowed to cool slowly to form cocrystals in either open air or in hot air oven [19], for example, theophylline-citric acid cocrystals [25].

In this technique, solvent dissolving coformers are selected and dissolved, and finally, drug is scattered into it by dispersion homogenizer. The solution is then mixed with a proper solvent for the precipitation of coformer into the drug indomethacin-saccharin cocrystal powders, carbamazepine-saccharin cocrystal [26].

**Liquid-assisted grinding method**

Liquid-assisted grinding is another commonly used method to form cocrystals. Besides providing faster rate of cocrystal formation than dry grinding, it is more reliable and suitable method as well. It is known to be ecofriendly method for industrial-level production due to less amount of solvent used. The process does not also depend on the temperature, and more importantly, it diminishes the chances of unwanted solvate formation, adefovir dipivoxil-glutaric acid cocrystal [27] and quercetin-succinic acid cocrystal improves solubility and dissolution rate by 1.62 and 1.25, respectively.

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Fig. 1: Techniques of cocrystal formation [5]
Solvent drop grinding
This method involves incorporation of API and coformer with the addition of suitable solvent. The solvent is added in drops with continuous stirring. The solvent used behaves as a catalyst which enhances crystal formation. This technique is also suitable for the synthesis of amorphous cocrystals. Example includes carbamazepine-nicotinamide coamorphous crystals.

Cooling crystallization method
It is less frequently applied method for the cocrystal formation. It is generally slow and time-consuming process as compared to other techniques, for example, darunavir-succinic acid cocrystal. In this, there is an improvement in solubility, dissolution, and micrometric properties than its individual drug darunavir [28].

Reaction crystallization method
This technique is mainly employed for quick formation of cocrystals at the macroscopic and microscopic level at a room temperature in which cocrystallization and nucleation are based on their solubility and cocrystal formation. Drug and coformer are solvated separately in either methanol or other suitable solvent and finally mixed together for crystal formation under its solubility limit. To determine stoichiometry of the complex, precipitates are collected and examined by high-performance liquid chromatography [29].

Ultrasound-assisted solution method
This technique is used for the nanocrystal preparations in which drug and coformers are dissolved in an appropriate vehicle (solvent). Solution is placed in a sonicator to form turbid, and temperature is maintained to prevent fragmentation and degradation. Solution is kept overnight for solvent evaporation and cocrystal formation [30].

Spray dying method
It is very commonly employed method for the preparation of cocrystals because of its quick, continuous, and single step process. In this technique, solution containing API and coformer is allowed to evaporate over hot air stream. This technique is relevant to scale up and more user friendly, for example, sulfadimidine/4-aminosalicylic acid cocrystals [31].

| S. No. | Drug | Coformer | Preparation technique | Property improved |
|-------|------|----------|-----------------------|-------------------|
| 1.    | Fluoxetine HCl | Benzoic acid Fumaric acid Succinic acid | Solvent evaporation | Dissolution rate |
| 2.    | Ibuprofen | 4,4-Diprydyl Nicotinamide | Solvent evaporation | Solubility was increased by 62 times in suspension form Enhanced dissolution and solubility rate as amorphous form |
| 3.    | Itraconazole | Malic acid Tartaric acid Succinic acid | Solvent evaporation | 3–45 times increased Solubility |
| 4.    | Norfloxacin | 4,4-Diprydyl | Solvent evaporation | Improved dissolution rate and bioavailability |
| 5.    | Piroxicam | Saccharin | Solvent evaporation | Increase in dissolution rate |
| 6.    | Acyclovir | Nicotinamide | Solvent evaporation | |

Fig. 2: Solid-state grinding. A=drug/active pharmaceutical ingredients B=Coformer/exipients

Fig. 3: Solvent evaporation technique

Fig. 4: Antisolvent method

Fig. 5: Solvent drop method

Table 1: Solvent evaporation technique for various drugs
Table 2: List of coformers

| S. No. | Ketoglutaric acid                  |
|--------|-----------------------------------|
| 1.     | Maleic acid                       |
| 2.     | Glutaric acid                     |
| 3.     | Maleic acid                       |
| 4.     | Oxalic acid                       |
| 5.     | Adipic acid                       |
| 6.     | Camphoric acid                    |
| 7.     | 4-hydroxybenzoic acid             |
| 8.     | Salicylic acid                    |
| 9.     | 1-hydroxy-2-naphthoic acid        |
| 10.    | Ketoglutaric acid                 |

EVALUATION AND IDENTIFICATION OF CO-CRYSTALS

Fourier-transform infrared spectroscopy: It is widely used process for the prediction and determination of chemical conformation, intermolecular interactions, and communion study between API and coformers. This method is quick, nondestructive, prone to changes in molecular structure and can also detect a functional group.

Differential scanning calorimetry (DSC): It is used for the determination of cocrystal formation, determined by the existence of exothermic crest followed by endothermic crest in the DSC spectra [32]. The cocrystal formation is determined by the presence of crest (peaks) present in the compound. It is also useful for determining the melting point, polymorphic nature, glass temperature, heat of fusion, and exothermic or endothermic behavior of a compound or a molecule [37].

Thermal gravimetry method
This method is useful for determining the sample weight under the influence of temperature for a specific period of time. It gives exact drying temperature along the various reaction steps involved in the component. It is used for the prediction of stability, purity, compatibility, and solvates/hydrates forms of cocrystals [38].

Terahertz time-domain spectroscopy
This technique is similar to that of powder X-ray diffraction (PXRD) for the characterization and identification of cocrystals. It is useful for differentiating supramolecular structures, chiral, and racemic molecule present in a given sample [39]. Example includes cocrystals of theophylline with different conformers [40].

Solid-state nuclear magnetic resonance (SSNMR)
SSNMR is generally used for characterization and identification of various solid forms of pharmaceutical products including the cocrystals. The basic principle used in SSNMR is the nuclei shift by irradiation that differs it from the excipients. The common examples are 13C, 31P, 1H, and 19F [41]. By this quantitative and qualitative technique, we can determine the molar ratio of reaction mixture and type of hydrogen atom present in a given molecule [42,43].

PXRD
It deals with the study of crystalline behavior of a powder or a drug sample. Bolla et al. carried-out analysis of acetaminophen cocrystals using these analytical techniques. They revealed the crystalline cell dimension, purity, structure, and texture of this bulk sample [44].

Dissolution studies
It can be defined as “the quantity of drug substance that changes into a solution in a unit time in specific conditions of liquid/solid interface, solvent composition, and temperature.” In-vitro dissolution study
of any solid drug is carried out to evaluate the dissolution efficacy of formulated drug [45].

**Stability study**

It is also one of the potent parameters for the evaluations of cocrystals as it gives information about different climatic storage conditions and shelf life of the drug or drug products. There are various parameters that affect the stability of drug such as humidity, light, and temperature [46].

Hansen Solubility study: Hansen solubility parameter is one of the potent tools to predict the miscibility of a drug and coformer in crystal formation or with excipients/carriers. It can also predict compatibility of pharmaceutical materials and its study is also useful for the pre-formulation and formulation of tablets [47]. The cohesion energy is utilized to predict physiochemical properties such as melting point and solubility of a compound [48]. Cocrystals are held together by a weak hydrogen bonding and are miscible at the molecular level. In solubility study, different types of solvents are used such as water, buffer solutions of different pH, stimulated intestinal fluid, and gastric fluid. It is one of the potent parameters of drug testing for drug development. The solution stability has been performed in various cocrystals such as carbamazepine/saccharin cocrystal, succinic acid cocrystal, indomethacin-saccharin cocrystals, and glutaric acid cocrystals.

**APPLICATIONS OF COCRYSTALS**

**Bioavailability**

It is a potent parameter to determine the amount of drug that reaches into the systemic circulation, and there is lesser number of animal studies on bioavailability of cocrystals. Cocrystals are developed to improve its bioavailability, solubility, permeability, dissolution, and other physiochemical properties of an API with use of coformers, e.g., indomethacin-saccharin cocrystals have improved bioavailability than its pure API drug, indomethacin, cocrystals of glutaric acid and 2-[4-(+chloro-2-fluorphenoxy) phenyl]-pyrimidine-4-carboxamide had improved oral bioavailability [49].

**Solubility**

Low solubility drug can be improved with cocrystal formation in which solubility is enhanced by a conformer of highly solubility. Example: Meloxicam-aspirin cocrystal a NSAID drug with low aqueous solubility and high permeability had slow onset of action (>2 h). The issue was solved with cocrystal formulation in the form of faster dissolution, improved oral absorption, and quick/early onset of action. In this, aspirin was used as conformer [50]. The solubility issue of both drug ibuprofen and flurbiprofen was overcome with coformer nicotinamide forming cocrystal with each drug. Tabulating behavior and moisture sorption increased dissolution rate by 8-fold and 5-fold, respectively. Likewise, AMG 517 cocrystal decreases the dose by increasing dissolution rate of active moiety. The solubility issue of itraconazole was overcome by forming a cocrystal with malic acid and dissolution rate was also improved [51].

**Stability**

Temozolomide (TMZ)-succinic acid, TMZ-malic acid, and TMZ-tartaric acid cocrystals, an anticancer drug, are known to be more stable at pH 2-6 than the puredrug. With temperature 40°C and relative humidity 75%, TMZ started degrading after a week except TMZ-succinic acid and TMZ-oxalic acid. This stability pattern was revealed using PXRD [52].

**Melting point**

It is the temperature at which solid material is at equilibrium with liquid phase [53]. The melting point of a drug is also related to its solubility, stability, tablet ability, flow property, and processability of a drug formulation. The cocrystal form of drug generally decreases the melting point than its pure drug and coformer. The melting point of hexamethylenedisocetamide (anticancer drug)-dicarboxylic acid cocrystals had reduced melting point than its pure drug along with the improvement in the physicochemical properties of a drug [54].

**Tablet stability**

The proper and elegant tablet formulation is also one of the most potent parameters of a cocrystal development. The cocrystals of efavirenz-adipic acid and cocrystals of efavirenz-lactic acid show 3-3.5-fold improvement in the solubility along with its tablet property [55]. The leflunomate-nicotinamide cocrystals prepared with ethanol by solution technique had improved tabletting property like plasticity and flowability [56].

**COFORMER**

Coformers are considered as inert, pharmacologically safe component for the formation of cocrystals. The selection of coformer is one of the most tedious tasks in cocrystal development and synthesis. They are generally used to enhance various properties of a drug such as microemericits, stability, and dissolution pharmacological depending on the nature and category of drug to which they belong. It may be either a drug or excipient [56]. These coformers are therapeutically or pharmaceutically safe, inert, economical, and are easily available.

**TYPES OF COCRYSTALS**

**Molecular cocrystals**

These cocrystals contain only neutral components (coformers).

**Ionic cocrystals**

In ionic cocrystals, the dominant interaction has an electrospheric nature with the possible additional contributions of hydrogen bonds between common donor and acceptor (OH, NH, O, N, etc.). The best example of this is ionic cocrystals of sodium chloride with carbohydrates [57]. Gilds et al. studied on the organic cation halides based on ionic cocrystals and fluoxetine hydrochloride ICCs with a group of carboxylic acid coformers was also invented by him. Tetracycline ICCs with improved performance, sacaglitin hydrochloride with improved stability, and streptomycin acid salts with alkaline earth metals are some of examples of ICCs [58].

**Multidrug cocrystals**

These are crystalline solid form of materials made of two or more than two therapeutic molecules in a stoichiometric ratio. These are also known as drug–drug cocrystals. It has become a newer approach for drug development [59].

Several crystal structure prediction programs were designed to find the crystal structure of an organic molecule, starting from the chemical diagram. However, the existence of polymorphism, the appearance of different crystal structures containing only the same molecule, immediately shows that some crystal structures are not the thermodynamically most stable. Molecules often they crystallize first in a metastable polymorph and then can be transferred into stable form [60].

**CONCLUSION**

Crystallization is one the noble approaches for improving the various parameters of active pharmaceutical ingredients such as stability, solubility, micrometrics properties, dissolution bioavailability, and pharmacokinetic properties by proper selection with coformers. The selection of coformers must be as per the United State Food and Drug Administration guidelines which do not produce any toxic effect with the drug. The techniques used for the preparation of cocrystals must be easy, safe, saleable, ecofriendly, and productive. Cocrystals also provides useful parameters such as improvement in permeability of poorly soluble drugs and better tabletting property in case of poor tablet forming drugs.

**AUTHORS’ CONTRIBUTIONS**

The author declares that all the authors listed in the paper have contributed to the literature review for this paper.

**CONFLICTS OF INTEREST**

No conflicts of interest are associated with this work.
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