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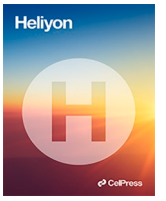

Review article

A review on advancement of cocrystallization approach and a brief on screening, formulation and characterization of the same

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ABSTRACT

The objective of this review is, to discuss recent advancements in screening methods for co-formers, evaluation cum confirmation methods and co-crystallization with examples.

Co-crystals are considered as a new form of an old drug entity. Co-crystals improve the stability, hygroscopicity, solubility, dissolution, and physicochemical properties of pure drugs without altering chemical and pharmacological properties.

Advancement in co-crystal formulation methods like electrospray and laser-irradiation methods are showing potential for solvent-free co-crystallization and tends to give better yield and lesser loss of materials. Screening methods are also transformed from trial and error to in-silico methods, which facilitate the selection process by reducing the time of screening and increasing the number of co-formers to be screened. Advanced evaluation methods like Raman and solid-state NMR spectroscopy provide a better understanding of crystal lattice by pinpointing the interaction between drug/co-former molecules. The same evaluation methods can also differentiate between the formation of salt and co-crystals.

Co-crystals are helping open a new door in pharmaceutical industries in the field of formulation for the improvement of physicochemical properties in existing old molecules and several new molecules. With a motto of "making a good drug better", co-crystals show scope for vast research and give researchers an ocean of opportunities to make the impossible, possible.

1. Introduction

Most of the new drug entities developed in pharma industries have issues with solubility and physicochemical properties like flowability, hygroscopicity, particle size, crystal lattice, density, taste, and thermal stability [1,2]. Through various methods, it is possible to improve all these limitations of most of the APIs. On top of that, these methods make formulation cost-effective. Improvement in dissolution and solubility of APIs can also reduce the required dose and chances of toxicity by dose dumping in many cases. The discovery of the new drugs comes with several complications implicating the situation of crisis in pharma industries. More than 40 % of marketed drugs are poorly soluble and more than 60% of new drug entities coming out from pharmaceutical chemical laboratories lack aqueous solubility because of the increased molecular size and lipophilic nature of drug molecules [2,3].

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Other major challenges faced by pharmaceutical industries are the expiration of patent rights and revenue loss from it. The emerging molecules can't produce enough revenue due to generic competition in the global market. That is why it is a broad topic of prompt interest to overcome this type of difficulty. To overcome these types of problems, first of all, we need to extend the patent rights, molecules need to be modified without changing their pharmacological effectiveness and by producing a new drug form, which possesses better pharmaceutical physicochemical properties than its parent molecule [4]. For that researchers are finding new solid lattice forms with other APIs or excipients of an old chemical entity by methods like salification and co-crystallization. These methods give promising outcomes by manipulating various physicochemical properties of the final form of APIs, without altering the pharmacological effectiveness of actual APIs. In the last two decades, many researchers have had to dig up the field in an attempt to screen, isolate, and study multi-component systems of various pharmaceutical drug forms in the hope of enlightening the future path for the betterment of various physicochemical properties of stubborn drugs with poor solubility and bioavailability. With this vision in mind, various solid forms of active pharmaceutical ingredients were studied, like salts, solvates/hydrates, polymorphs, and co-crystals. Despite being different forms of the same drug, each of them may exhibit different pharmaceutical properties [5]. This requires broad screening to find optimal and stable solid-state forms in the early phase of the development of a drug [6]. In the process of formulation, the ease of manufacturing and thermodynamic stability is majorly concerned with the development of the pharmaceutical product. The most thermodynamically stable form of drug entity needs to be selected appropriately [2].

From all the multicomponent systems mentioned above, we are going to discuss particularly recent advancements in co-crystals in this review article. Co-crystals are a prominent approach for the improvement of physicochemical properties [7–10] [7–10] [7–10]. Unlike salts, it does not need ionic bonds to form co-crystals [2,11]. Non-ionizable molecules can form co-crystals with appropriate co-formers. The only limiting factor for co-crystals is safety requirements. Co-crystal co-formers should be safe for human consumption. All salts and co-crystals are eligible for gaining intellectual property rights and also for obtaining commercial advantage. One more advantage for co-crystals is that the patent approval will be easy due to already present data of the previous pharmaceutical product [2,12]. The co-crystals have yet not gained impactable market value but give a promising prospective image for the near future.

Under a multi-component system, co-crystals can be divided into various types like drug-co-former co-crystals, drug-drug co-crystals, drug salt-co-former co-crystals, three-component systems (drug-drug-co-former). Formulation of co-crystals can be done by various methods like neat grinding, liquid-assisted grinding, cooling crystallization, solvent evaporation, fusion, anti-solvent addition precipitation, SCF technology, ultrasound-assisted solution crystallization, electron spray and spray congealing.

In co-crystal formation, the selection of a co-former is a very important step for the formulation of co-crystals [13]. The process of selection of co-former can be done by various computer software like cosmologic® and also can be done by trial and error method. Screening by software like Cosmologic gives a preliminary idea about the possibility of the formation of co-crystals with various co-formers. The software works on the difference between the enthalpy of pure drug, pure co-former, and the mixture of drug-co-former in virtually sub-cooled liquid. The resultant highly negative value of the difference of enthalpy is selected for the formulation of co-crystals. This value mainly depends upon the co-former enthalpy value and drug-co-former mixture enthalpy value [14].

Characterization of co-crystals can be done by different methods like crystallography (single crystal/powder x-ray diffraction method), thermal analysis (Differential scanning calorimetry, hot stage microscopy), and spectroscopy (Raman, IR, Solid-state NMR spectroscopy). Among all the methods, PXRD gives the best results and is more reliable for confirming co-crystallization than other methods of characterization and Raman spectroscopy can provide final confirmation by identifying pure drug, co-former, and co-crystal presence in the final product by color coding each material.

This review contains a detailed discussion of various types of co-crystals, methods for co-crystallization, selection of co-formers, characterization and confirmatory study of co-crystals, and understanding of the working principles of various essential software related to Co-crystallization.

2. Definition

2.1. Co-crystals

Co-crystals can be defined per the USFDA as "crystalline material composed of two or more different molecules, one of which is the active pharmaceutical ingredient, in a defined stoichiometric ratio within the same crystal lattice that is associated by non-ionic and non-covalent bonds." [15].

2.2. Co-former

As per USFDA co-former can be defined as "a component that interacts non-ionically with the active pharmaceutical ingredient in the crystal lattice, that is not a solvent (including water), and is typically non-volatile." [15].

3. Method for co-crystallization

Methods categorized as conventional methods are further classified as solid-state co-crystallization and liquid (solution) co-crystallization. In the solid-state co-crystallization method, the pure shear force is used to facilitate the formation of co-crystals. This is known as the neat/dry grinding method. With the addition of a minute amount of solvent, neat grinding can be modified to

liquid-assisted grinding. In solution crystallization, an excess amount of solvent is used to solubilize components (active pharmaceutical ingredients and co-crystals former). Co-crystals are obtained in the form of precipitate in the anti-solvent addition method and dry residue in solvent evaporation and cooling crystallization methods. The next method is fusion co-crystallization. In this method, a physical mixture of active pharmaceutical ingredient/s and co-former is heated to melt both the components and cooled to obtain fused single material as co-crystals. Various novel methods for co-crystallization involve the spray drying method, microwave-assisted co-crystallization, supercritical fluid technology, ultrasound, and ultrasound-assisted solution crystallization, electrospray method, laser irradiation, and spray congealing method.

3.1. Co-crystals by grinding

3.1.1. Neat grinding

Neat grinding is a solvent-free method, in which a physical mixture of materials in the stoichiometric ratio is pressed and crushed manually in mortar-pastel or by mechanical means like a ball mill or vibrational mill. The mechanism of the co-crystal formulation is size reduction leads to the surface interaction of co-crystal components. This leads to the induction of covalent bonding or supramolecular reactivity among the target molecule and co-former. Neat grinding is a viable alternative for solvent-based co-crystallization techniques. In some cases, the neat grinding method shows superior selectivity in comparison to solvent-based co-crystallization methods. Generally grinding time in this method is 30 min to 1 h. Neat grinding is a simple, fast, and convenient method for co-crystal formation [5,16].

Yuta Otsuka and co-workers obtained co-crystals of caffeine and oxalic acid by the neat grinding method. After around 10 min of mechanical grinding, chemical equilibrium was achieved in the system. This study suggests that the importance of rotation speed is more than that of the temperature for the production of co-crystals. With the increase in speed, co-crystal content also increases [17].

3.1.2. Liquid assisted grinding (LAG)

Liquid-assisted grinding (LAG) is a modification of the neat grinding method. Liquid-assisted grinding involves the addition of a very small amount of solvent to facilitate the formation of co-crystals and the solvent persists only for the grinding process period. Solvent performs the role of a catalyst by assisting co-crystallization. Liquid-assisted grinding is a more efficient method than neat grinding, as the solvent present in the grinding process works as a catalyst for co-crystal formation by wetting the surface of co-crystal components [18].

Fang Liu and co-workers formulated isoniazid co-crystals utilizing the liquid-assisted grinding method. Isoniazid-syringic acid co-crystals demonstrate the elimination of hepatotoxicity of isoniazid, which is observed in a hepatotoxicity study in rats. Co-crystals exhibit a sustained release mechanism for the slow release of isoniazid. Syringic acid has very poor solubility and due to that poor bioavailability. In *in vitro* study, sustained release shown by co-crystals might be due to decreased solubility of isoniazid and improved solubility of syringic acid in the isoniazid-syringic acid co-crystal system in contrast to the physical mixture of components. This contributes to sustaining the release of isoniazid from the co-crystal system [19].

Terence J. Noonan and co-workers successfully obtained 3 different imidazopyridine drug lead (MMV) co-crystals with adipic acid, fumaric acid, and glutaric acid co-formers. All co-crystal formation was confirmed by PXRD, FTIR, and DSC characterization techniques. The kinetic solubility study shows improvement in the solubility of all three co-crystals as compared to untreated MMV. MMV-ADI co-crystals (2:1) exhibit only the spring approach in drug release study. While MMV-GLUT (1:1) and MMV-FUM (2:1) co-crystals show spring and parachute approaches in the drug release study. The study also suggests that melting point determination can also be implemented for screening of eutectic mixtures, salts, and co-crystal products [20].

3.2. Co-crystals by solvent evaporation method

In this method of co-crystal formation, an excess amount of solvent is utilized for solubilization of the stoichiometric ratio of drug and co-former. Then evaporate either at room temperature [21–23] [21–23] [21–23] or by applying a vacuum to accelerate the process of drying [24,25]. The solvent evaporation method is generally used for the formation of a single crystal of multi-component systems for characterization by the single-crystal x-ray diffraction method. The solvent evaporation method has several disadvantages like the use of a large amount of solvent and limited scalability. But, it can be used for lab-scale preparation, which doesn't require any expensive instruments. The solvent evaporation method provides high-quality and high purity co-crystals [26].

Wen Li and co-workers prepared co-crystals of baicalein with theophylline co-former by the solvent evaporation method. Obtained co-crystal exhibits a significant increase in performance in *in-vitro* as well as *in-vivo* evaluations [26].

José Venâncio Chaves Júnior and co-workers prepared ferulic acid-nicotinamide co-crystals by rapid solvent evaporation technique Co-crystals exhibit a 70 percent increase in ferulic solubility and even better dissolution at pH 6.8 as compared to the physical mixture [27].

3.3. Co-crystals by anti-solvent addition crystallization

In the anti-solvent addition method, co-crystal components are dissolved in a single suitable solvent. After the complete solubilization of components, an anti-solvent liquid is added to obtain co-crystals in the form of a precipitate. In the anti-solvent addition method selection of a pair of solvent and anti-solvent is a critical step. Criteria for liquids to be selected as solvent and anti-solvent are, that they should be miscible with each other and the selected solvent should be capable of solubilizing both the components of co-

crystal [28–30].

In-Chun Wang and co-workers obtained carbamazepine-saccharine co-crystals by the anti-solvent addition method. The specific ratio of drug and co-former under optimal conditions shows the most desirable purity and crystal quality. The experiment suggests that the selection of solvent and anti-solvent and the ratio of co-crystal components are very critical for forming co-crystal by the anti-solvent addition method [31].

3.4. Co-crystals by cooling crystallization

In the cooling crystallization method, the solution is heated and allowed to stabilize for some time. After the stabilization of the solution, cooling is started at a suitable temperature drop rate (°C/min) to form a co-crystal in the solution. Crystallized product is collected by vacuum filtration. The temperature of heating varies with the type of solvent and co-crystal components [32].

Nan Hee Chun and co-workers demonstrated the potential of cooling crystallization for the formulation of indomethacin-saccharin (IMC-SAC) co-crystals. In this method, the solution was heated at 45 °C and allowed to settle for 30 min. Then cooling started at the rate of 1 °C/min to achieve 15 °C temperature using a cooling circulator. This experiment was performed to check the effect of combining two methods of Co-crystallization on co-crystal formation. The use of the anti-solvent method with cooling crystallization results in an increase in the degree of supersaturation. Which leads to the growth of co-crystals via pure IMC-SAC nucleate without dissolution or transformation. It gives a higher yield and better crystallinity to co-crystal products [33].

3.5. Co-crystals by fusion method

Drug and co-former are melted separately or in a physical mixture and mixed uniformly to get a homogeneous mix of components. Melted mass allowed cooling down at room temperature to obtain the solid-state form of co-crystals. This can also be performed by using the hot-melt extrusion method for Co-crystallization. Hot-melt extrusion spontaneously melts and mixes material via a heated screw extruder. The main advantage of this method is the continuity of the process, doesn't require solvent, fast operation, reduction in waste of materials, and high conversion as compared to solvent-based methods. The only disadvantage of this method is, that it can't be utilized for heat-sensitive materials [34,35].

P. Barmpalexis and co-workers carried out a study in which carbamazepine-nicotinamide and ibuprofen-nicotinamide co-crystals were formulated with the aid of soluplus (SOL) as matrix polymer using a melt mixing technique. Soluplus co-crystal was prepared by mixing co-crystal with soluplus at various ratios. Components were mixed and heated at 170 °C for CBZ/NCT-SOL and 140 °C for IBU/NCT SOL, using mortar-pastel until a homogeneous mixture was observed. The study suggests cooling of the melted sample showed the formation of crystals in high API/co-former concentration, while the low concentration sample remained amorphous. It is probably due to the contribution of soluplus as a kinetic barrier to drug recrystallization [34].

3.6. Co-crystals by spray drying

Spray drying is a single-step continuous scalable process. This process is used for the preparation of solid powder from liquids like solution and suspension using spray dryer equipment. It is useful in the production of pure co-crystals from congruent as well as incongruent saturating solutions. But, spray drying requires costly equipment which requires high maintenance to work efficiently and a skillful person to operate it. The method is used for the formulation of amorphous solids. It is sometimes difficult to produce crystalline phases from co-crystal components [36,37].

David Walsh and co-workers prepared sulfadimidine 4 aminosalicylic acid co-crystals by the spray-drying method. The study suggests the importance of spray drying parameters like flow rate, and heating temperature for obtaining good-quality drug co-crystals [38].

3.7. Co-crystals by supercritical fluid technology

Supercritical fluid technology has numerous advantages over other methods of Co-crystallization like an environment-friendly solvent, drying step elimination, no presence of residual solvent in the final product, micro-sized particles being obtained and the process can adapt to continuous production [39]. Supercritical fluid technology has wide number of modifications in the past few years like rapid expansion of supercritical solution (RESS), supercritical anti-solvent crystallization, supercritical fluid enhanced atomization (SEA), atomization, and anti-solvent crystallization (AAS), gas anti-solvent crystallization (GAS). All modifications are discussed in detail in the review work of Concepeion Pando et al. [40].

Marcela M. Ribas and co-workers prepared curcumin- N-Acetylcysteine co-crystals using supercritical fluid technology. Obtained products possess high purity and quality co-crystals [41]. (41)

Napada Wichianphong and co-workers have successfully prepared mefenamic acid-nicotinamide co-crystals using the gas anti-solvent method. The study suggests the ratio of drug and co-former and the percentage of drug saturation had a significant effect on co-crystal dissolution time [41].

Luis Padrela and co-workers produced co-crystals of various drug-using SEA technologies. The size distribution of the obtained product lies between the 0.3 to 10-μm range. The study demonstrates the potential of supercritical fluid technology in the screening

and formulation of co-crystals [42].

3.8. Co-crystals by ultrasound-assisted solution crystallization

Ultrasound-assisted solution crystallization uses ultrasound pulses to generate nuclei during the drug crystallization process. Ultrasound creates voids or air bubbles in liquid while imparting cycles of compression and thinning to the inner part of the liquid. During the compression cycle, air bubbles absorb more energy and collapse violently in liquid. This energy release increases the temperature of the liquid. Air bubble contents are compressed and result in the formulation of co-crystals. This leads to the precipitation of co-crystals from a homogeneous solution of co-crystal components [43].

Suyog Aher and co-workers formulated caffeine-maleic acid co-crystals using ultrasound-assisted solution crystallization. The USSC method has altered the supersaturation condition of components in liquid to facilitate the generation of co-crystal nuclei [44].

Prafulla Apshingekar and co-workers also produce caffeine-maleic acid co-crystals using the green USSC method. This study utilized an aqueous medium for the formation of co-crystals. The use of ultrasound in the formulation of co-crystal can reduce the non-congruency of components and can facilitate the solubilization of co-crystal components in the aqueous medium. The solubility of caffeine in aqueous medium was increased from 0.104 ± 0.011 to 0.642 ± 0.071 μmol/ml. Likewise, the solubility of maleic acid was increased from 3.448 ± 0.299 to 7.327 ± 0.613 μmol/ml due to the presence of ultrasound pulses. The study also suggests the use of ultrasound in an aqueous solution, to narrow the region of co-crystallization in the ternary phase diagram for the formulation of caffeine-maleic acid (1:1) co-crystals. Other co-crystals in the ratio of 2:1 can obtain a broad region in a ternary phase diagram. However, in this ratio, co-crystals exhibit poor stability due to dissociation into individual components. The responsible factor for dissociation is the large difference in solubility of components in the selected solvent [45].

3.9. Co-crystals by microwave-assisted Co-crystallization

The microwave-assisted co-crystallization method is a clean, economical, fast, and scalable method. This can give higher yields by utilizing a shorter reaction time as compared to the conventional heating method. Microwave as a heating source increases the rate of co-crystal formation in comparison to the normal heating process. In this method, co-crystal components and solvents are placed in a microwave radiation reactor at suitable temperatures and pressure for a specific time to obtain the desired co-crystal product [46].

Dipali Ahuja and co-workers prepared sulfamethazine co-crystals using the microwave-assisted co-crystallization technique. This study suggests that microwave as a heating source increases the rate of co-crystal formation in comparison with the normal healing process. The study demonstrates the potential of microwave-assisted co-crystallization for scaling up the process from 0.2 to 20 gm production capacity without altering product quality [47]. These advantages can be utilized in industries for faster formulation speed and for obtaining a good quality product.

3.10. Co-crystals by electrospray method

Electron spraying is a simultaneous process of droplet formation and electric charge generation on droplets. In this formulation method, a spray of co-crystal components solution flows out from the capillary nozzle. The spray maintains a high potential throughout the electric field causing the elongation of the droplet to form a jet. These droplets are dried and formulate powder particles which are to be collected by a charged particle collector. Fig. 1 shows step by step process of electro spraying and co-crystal generation in electrospray method [48].

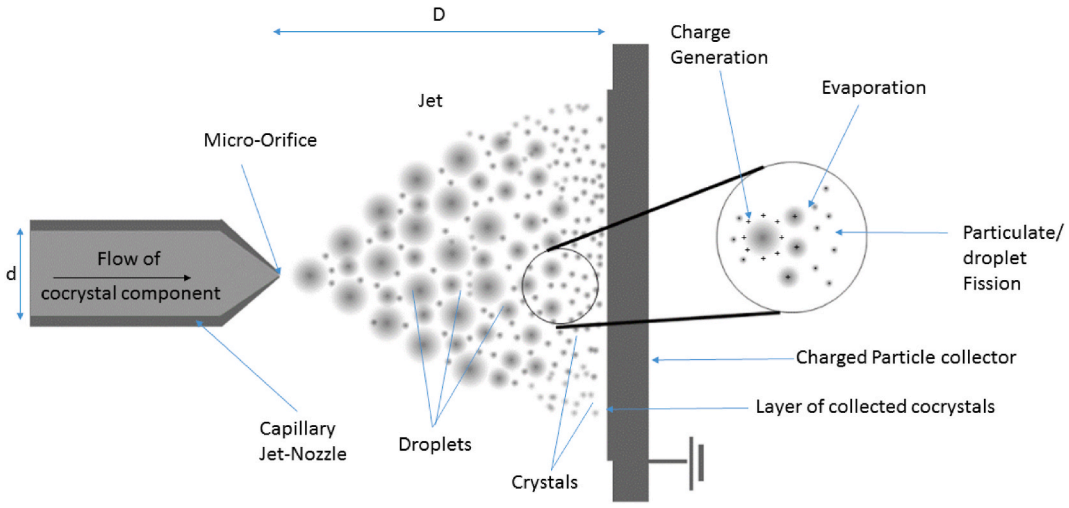

Fig. 1. Electrospray cocrystal formulation mechanism.

Sharvil Patil and co-workers demonstrated the potential of the electrospray method to formulate co-crystals. Forskolin-nicotinamide co-crystals show a significant decrease in particle size as compared to pure Forskolin and 2.74-fold increases in solubility as compared to Forskolin. This study suggests needle shape of co-crystals provides an enormous increase in surface area and reduced particle size by electrospray method resulting in an increase in the dissolution of Forskolin-nicotinamide co-crystals in comparison with co-crystals obtained by other methods [48].

Shahram Emami and co-workers formulated naproxen nicotinamide co-crystals using electrospray. NPX-NIC co-crystals were formulated in 2:1, 1:1, and 1:2 ratios. Only NPX-NIC co-crystal with a ratio of 2:1 was successfully formulated with high purity. Other ratios of co-crystal components give a product containing a high amount of impurities. The collection time of co-crystals plays a major role in the conversion of amorphous forms into crystalline forms. Collection of product, immediately after the process, shows the presence of a small amount of amorphous form. The collection of the product after 24 h shows a complete conversion of amorphous form into crystalline form. The working distance of 20 cm was optimized. Therefore, the ratio of drug and co-former and electrospray conditions (working distance and collection time) are critical factors for the formulation of high-quality co-crystals [49].

3.11. Co-crystals by laser irradiation

As shown in Fig. 2, laser irradiation imparts high-level radiation energy to the physical mixture of co-crystal components for a very short time. This results in rapid heating and melting of co-crystal components. After the completion of heating, cooling is done for recrystallization in the form of co-crystals. For this method, the co-former should be sublime material, to favor the nucleation process through the vapor phase which is a probable formulation mechanism [50].

Varin Titapiwatanakun and co-workers demonstrated the potential of the laser irradiation method for the synthesis of caffeine-oxalic acid (2:1) co-crystals. This experiment used a CO_2 laser for imparting radiation energy to co-crystal components. The study observed that the speed and power of the laser is the main factor that affects the production of high-quality co-crystals. Low power laser is not sufficient for increasing enough temperature to melt co-crystal components, while high power laser can degrade the co-crystal components. During the experiment, the speed and power of the laser were in the range of 50–60 percent of the maximum achievable value by the instrument [51].

3.12. Co-crystal by spray congealing

Spray congealing is a solvent-free green method for the synthesis of co-crystals. A stoichiometric mixture of co-crystal components is melted in a beaker and spray congealing is performed by a modified two-nozzle spray dryer. Schematic diagram in Fig. 3 shows flow of liquid material through instrument. A spray dryer is used for the atomization of melted mass. Solidification is favored by a concurrent stream of nitrogen and solid co-crystals are collected from the cyclone separator [52].

Íris Duarte and co-workers demonstrated the potential of spray congealing in the formulation of caffeine-salicylic acid co-crystals. The obtained co-crystals were compact and spherical. Co-crystals adhered to each other in aggregate form. In this study, it is observed that in situ adjustments of co-crystal properties like purity, shape, size, and flow properties can be done by varying the temperature difference (°C) and feed atomization rate (L/min) [53].

4. Co-former selection methods

Co-former selection is a very crucial and critical step in the formation of Co-crystals [54,55]. Changes in the physicochemical properties of co-crystals depend upon the suitability of the co-former. Appropriate selection of co-formers improves the physicochemical properties of co-crystals and also a biased selection of co-formers can worsen the same. The drug-to-co-former ratio also

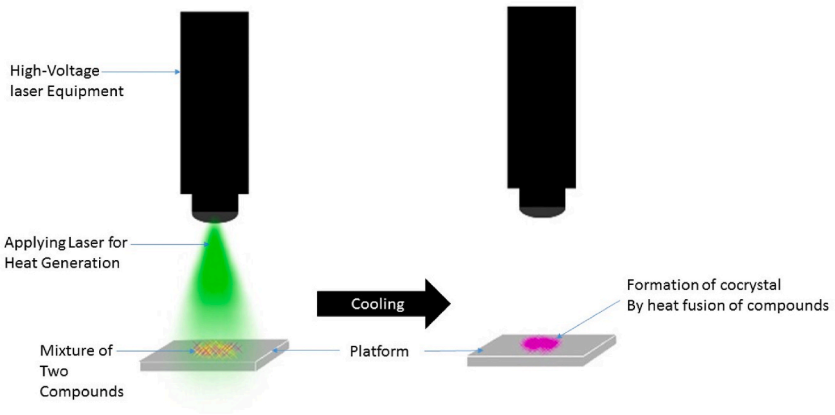

Fig. 2. Co-crystals by laser irradiation.

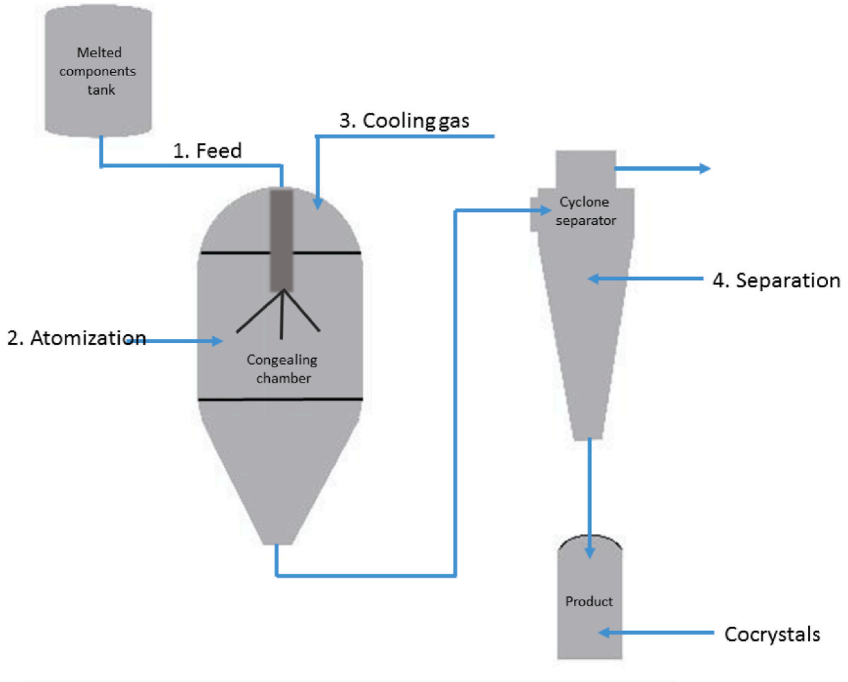

Fig. 3. Spray congealing instrument (spray dryer).

affects the physicochemical properties of final co-crystals [56]. Therefore, various selection methods are used to screen out suitable co-formers for specific drug molecules [57]. There are seven different methods currently available for preliminary screening of co-formers.

4.1. pKa based model

The formation of co-crystals can be determined by the transfer of protons between acidic and basic functional groups of co-crystal components [58]. By determining the ΔpKa value, it is possible to predict the formation of co-crystals or salts. The validation and quantization of the pKa rule have been performed by calculating pKa values of 6465 crystalline components contacting ionized and non-ionized acid-base pairs in the Cambridge structural database. A linear relationship is obtained between ΔpKa and proton transfer probability between acid-base pairs and that has been derived for crystalline complexes with ΔpKa between −1 and 4. For co-crystal formation value of the ΔpKa of components should be between 0 and 3 [59].

In study performed by Mehta at el. on ketoconazole shows the formation of co-crystal (KTZ:PHBA) with para-hydroxy benzoic acid having ΔpKa of −1.6. The study suggests the formation of co-crystals while having a negative value of ΔpKa, is also possible [60]. European medicines agency have confirmed that ketoconazole is a dibasic agent and has two pKa values, which are 2.94 and 6.51. Taking both values into consideration, the first value shows a ΔpKa of −1.6 and the second value shows ΔpKa of 1.97, which is within the range of 0–3 [61]. Mehta et al. also concluded that the hepatotoxic activity of ketoconazole was also reduced due to para hydroxyl benzoic acid having hepato-protective properties by performing an in-vitro hepatotoxicity study on a normal Chang liver cell line. In-vitro antifungal activity study shows improvement in the fungicidal activity of KTZ:PHBA co-crystal as compared to ketoconazole and para hydroxybenzoic acid alone [60].

4.2. Cambridge structural database

Cambridge structural database is a computer-based approach for the determination of appropriate co-crystals forming pairs, reducing time for screening and reducing the cost of experiments. Cambridge structural database facilitates the statistical analysis of packing characteristics and provides info about general functional groups. Cambridge structural database is a validated tool for the selection of co-formers. In this [62] In CSD, a new network approach is utilized to gain a better understanding of co-formers which combine successfully to target molecules for the formation of co-crystals. Devogelaer et al. have developed an algorithm for screening of drug and co-former, which are suitable for forming inter molecular weak bonding. The algorithm finds an appropriate co-former from a cluster of selected co-formers which are already been screened by co-former degree *k*. In this selection module, Devogelaer et al. have selected two types of network approaches, monopartite and bipartite. Monopartite network approach will show results related derived from local community links and bipartite network approach will show results regarding two different molecules (common neighbor) interaction possibilities. A mix method, mono-bipartile method can be also used for finding simillar kind of

interaction between molecules, which can be helpful for determining the final possibility of crystal arrangement and sequencing of API and co-former in crystal lattice [63].

4.3. Hydrogen bonding

In co-crystal formation, non-covalent bonds like hydrogen bonds and van der Waals forces are responsible for the interaction between the target molecule and co-former. Among these forces, hydrogen bonding plays a major role in the formation of co-crystals [64,65]. Hydrogen bond propensity (HBP) and hydrogen bond energy (HBE) are knowledge-based prediction tools for the selection of co-formers. HBP is the probability of specific hydrogen bond formation which depends on the structural characteristics of the specific functional group. ΔHBP is calculated by the following equation [66].

$$\Delta HBP = (HBP_{API—COFORMER} - HBP_{API—API/COFORMER—COFORMER}) \quad (1)$$

If ΔHBP value is positive then co-crystal formation is possible among selected components and if the value is negative then co-crystal formation is not possible.

For HBE, it is calculated by using molecular electrostatic potential using density functional theory (DFT) ΔHBE is calculated by the following question.

$$\Delta HBE = (HBE_{API—COFORMER} - HBE_{API—API/COFORMER—COFORMER}) \quad (2)$$

If ΔHBE value is positive then co-crystal formation is possible and if negative then co-crystal formation is not possible among co-crystal components [66].

Although HBP provide best results regarding the prediction of co-crystal formation, the accuracy of method is low, when used alone. With other methodologies like molecular complementarity (MC), and hydrogen-bond energy (HBE), the accuracy of result can be improved [66].

4.4. Supramolecular synthon approach

As per the supramolecular synthon approach, the functional group present in target molecules and co-formers has a significant role in the synthesis of co-crystals [67,68]. A suitable functional group from the co-former is used for a specific target molecule functional group. Synthons are available as basic structural units in supramolecular, which are associated with non-covalent bonding. The supramolecular synthon approach is classified into two classes, homosynthon, and heterosynthon. Homosynthons are composed of the same functional group as in co-former and target molecules. Heterosynthons are composed of two different functional groups one in the co-former and the other in the target molecule. Generally, homosynthons are less favored than heterosynthons [69].

Tejender S. Thakur and co-workers predicted the crystal structure of 2 methyl benzoic acid-2 amino 4 methyl pyrimidine co-crystals by using the supramolecular synthon approach. The study suggests the supramolecular synthon approach provides useful structural insight and increases the success rate of crystal structure prediction. It is a robust method in thermodynamic system applicability [70].

4.5. Hansen solubility parameter

Hansen solubility parameter is an important method for measurement of the target molecule and co-former miscibility for multi-component systems like co-crystals. Hansen's solubility parameter suggests that the success rate of co-crystal formation is increased with the improvement in the miscibility of two components in the system [69].

4.6. COSMO-RS

The COSMO-RS fluid phase computation of thermodynamics is used for accurate and very efficient virtual screening of co-formers for co-crystallization. The screening is based upon the excess enthalpy (H_{ex}) property, which describes the miscibility of the co-former with API in an amorphous (subcooled liquid) state [14]. The following equation is used for the calculation of excess enthalpy:

$$H_{ex} = H_{AB} - X_m H_{pureA} - Xn H_{pureB} \quad (3)$$

Where H_{pure} and H_{AB} are molar enthalpies in pure and in mixture state with mole fraction of drug (m) and co-former (n).

Co-formers that have the highest chances of formation of co-crystals are determined by the lowest H_{ex} values [14,71,72].

The f_{fit} approach for screening co-crystals considers the flexibility of the target molecule and co-former by the number of rotational bonds present in co-crystal components. For the calculation of F_{fit} following equation is used.

$$F_{fit} \sim H_{mix} + a\,(\max(1, nrot_{API}) + \max(1, nrot_{COF}) \quad (4)$$

Where "a = 0.5102″ has been determined by a set of 300 target molecule co-former pairs from the literature. The kinetic nature of molecules provides more flexible components which may have a higher barrier for crystallization [14].

5. Characterization of Co-crystals

Several methods are employed for the characterization of co-crystals. In the past few years, this field has made much advancement in characterization technology. Characterization of co-crystals can be done by three main analysis methods namely single crystal and powder X-ray diffraction method (XRD & PXRD) [73], thermal analysis method (Differential scanning calorimetry [74] and Hot stage microscopy [75]), and spectroscopic methods (FTIR[77], Raman [76] & Solid-state NMR spectroscopy [77]). This section of the review deals with a brief description of characterization technologies and various current examples, which utilize these methods.

5.1. X-ray diffraction method (XRD) and powder X-ray diffraction method (PXRD)

XRD is a predominant and precise method for the identification and qualification of co-crystals. Single-crystal XRD is generally used for structural identification of large-size crystals (usually obtained by solvent evaporation method). Co-crystal obtained by the grinding method can't be characterized by single-crystal XRD. For that PXRD technology is used mainly for the identification of co-crystal formation. In PXRD, co-crystals show change in characterization peaks as compared to components of co-crystals. XRD techniques are also used for calculating the percentage yield of co-crystals by quantifying the percentage of co-crystals and co-crystal components in the obtained product [73].

Geetha Bolla and co-workers have determined the structure of acemetacin co-crystals by using the PXRD method. Three-dimensional data was obtained by PXRD technology to solve the crystal structure of acemetacin [78].

5.2. Thermal analysis method

In thermal analysis, there are mainly two methods available to carry out the characterization of co-crystals.

5.2.1. Differential scanning calorimetry (DSC)

Differential scanning calorimetry is an easy and convenient method for the characterization of co-crystals [79]. Co-crystals exhibit a significant change in endothermic and exothermic peaks of co-crystals comparison with pure components. The co-crystal DSC peak lies between the peaks of pure co-crystal components DSC peaks [80], which can be utilized for screening co-crystals by observing the DSC peak of the physical mixture of co-crystal components [74,81]. However, there are numerous example of formulated co-crystals that shows DSC peaks outside the range of API and co-former. This suggests the above-mentioned rule can't be used as a universal rule for conformation of co-crystal formation. DSC is a very rapid and efficient method for the characterization of co-crystals. It is a solvent-free method and requires a very small amount of sample to conduct a characterization study [82].

Enxian Lu and co-workers have screened 16 co-crystals by using the DSC method and nine of them are newly synthesized co-crystals, which have not been reported in any previous literature. Enxian Lu et al. has prepared a co-crystal of salicylic acid with coformer caffeine, which shows a melting point below the ones of salicylic acid and caffeine. The author suggests it is probably due to the eutectic nature of the mixture of two compounds [74]. Further research and data collection is necessary for this matter for the selection of coformer and conformation of co-crystals. Furthermore, the heat energy reading can also be utilized for the conformation of formulated co-crystals as the heat energy of co-crystals tends to reduce as compared to utilized API.

5.2.2. Hot stage microscopy (HSM)

HSM is popularly known for the characterization and screening of co-crystals. HSM allows users to observe recrystallization and crystal growth of melted components of co-crystal. Characterization and screening of co-crystals can be done by using Kofler mixed fusion method [83]. In this method at the interface of two components, the crystalline material is observed and that suggests the possibility of co-crystal formation between co-crystal components.

David J. Berry and co-workers have screened and characterized five API mixtures for the formation of co-crystals using the Kofler mixed fusion method by hot stage microscopy method [84].

Thermal methods of characterization and screening are rapid and convenient for co-crystals. The limiting factor of this method is that only thermally stable materials can be evaluated.

5.3. Spectroscopy

Spectroscopic characterization of co-crystals can be classified into two main types. The first is vibrational spectroscopy and the second is Nuclear magnetic resonance spectroscopy. The vibrational spectroscopic method is subdivided into FTIR spectroscopy and Raman spectroscopy. IR spectroscopy works on the absorption mechanism and Raman spectroscopy works on the scattering mechanism of spectroscopy. The NMR spectroscopy method is a very powerful tool to obtain detailed structural information about multi-component systems.

5.3.1. Fourier transform infrared spectroscopy

FTIR spectroscopy is a very efficient tool to identify the formation of co-crystals. The formation of co-crystals is confirmed by a change in vibrational energy peaks in spectra, mainly due to the formation of hydrogen bonding in the functional group of co-crystal components. FTIR spectra of pure co-crystal components and formulated co-crystals are compared for detection of co-crystal formation and structural elucidation [85].

Harry G. Brittain analyzed cinchona alkaloid-5 nitro barbituric acid co-crystals using FTIR spectroscopy. The study observes variations in absorption spectra of co-crystal and co-crystal components [86].

5.3.2. Raman spectroscopy

Raman spectroscopy is an in-situ monitoring and characterization method for co-crystal formation confirmation [87,88]. Raman spectroscopy exhibits better accuracy, precision, and sensitivity than the FTIR method. Raman spectroscopy can differentiate between co-crystal form and ionic form of multi-component systems. Evaluation of the formation of co-crystals is done by comparing the change in the oscillation of co-crystals in comparison to co-crystal components [76,87,89,90].

Yong Du and co-workers demonstrated potential applications of Raman spectroscopy in determining the co-crystal formation of nitrofurantoin and 4 aminobenzoic acid co-crystal components. Data obtained by Raman spectroscopy is useful for the discrimination of different multi-component pharmaceutical molecular solid systems [89].

K. C. Mullers at el. utilized color coding for fixed crystal patterns to identify raw ibuprofen and nicotinamide in the physical mixture and co-crystals and remaining coformer in the final product. Raman spectroscopic color-coded image of a final product shows the presence of formed co-crystals and some remaining coformer and no sign of the presence of pure ibuprofen [91].

5.3.3. Solid-state NMR spectroscopy

SSNMR has the potential to provide detailed structural information about organic and pharmaceutical co-crystals. SSNMR provides higher information content and high-yield data as compared to vibrational spectroscopy and PXRD methods. SSNMR is a non-destructive method and requires a very small amount of samples for data collection. Frederica G. Vogt [77] and co-workers examined several molecular complexes and co-crystals to understand the capabilities of SSNMR. This study determines the ability of SSNMR to prove molecular association and observe structural features like hydrogen bonding [92,93].

Li Zhao and co-workers demonstrated the potential of dynamic nuclear polarization enhanced SSNMR method for the characterization of co-crystals and salt forms. The NMR spectroscopy also measured the 1H–15 N dipolar coupling constants and H–N bond lengths more accurately. These parameters provide an unambiguous assignment of nitrogen protonation states and definitive differentiation of multicomponent systems as co-crystals or salts. This method can also solve major confusion of confirmation of the final product as co-crystals or as salts [93].

6. Conclusion

Co-crystals show promising results in the modification and improvement of the physicochemical properties of APIs. A broad range of methods of co-crystal preparation are available from lab-scale synthesis to industry-level continuous processes. This review gives a brief insight into various methods of co-crystal formation, co-former selection, and characterization of co-crystals with suitable examples. Co-crystals are continuously gaining the interest of pharmaceutical industries for the improvement of physicochemical properties and also due to the availability of patent rights for co-crystals which is vital for big pharma industries to generate revenues. It is expected that once the path for co-crystals formation is cleared and their benefits are proven, pharmaceutical co-crystals will become a more routine approach for pharmaceutical development.

7. Opinion of author

Various advanced methods do not use solvents and in place of that, it uses a high level of energy (mainly electrical). The main objective of green production is to reduce the impact on the environment by reducing or eliminating the use of organic solvents or greenhouse gases. However, advancements in formulation methods indirectly impact the environment by utilizing electrical energy from various conventional sources. Here necessity arises for comparison and calculation of the final impact of solvent utilizing methods and highly advanced methods. The formation of co-crystals using various novel methods which require costly equipment and even higher energy consumption is observed for the synthesis of the final co-crystal product. Improving the existing method like in the solvent evaporation method, controlling the evaporation process at a specific temperature and pressure may improve the formation of co-crystals without using any high-end equipment in the process. Green methods like the electron spray method and supercritical fluid technology can lower the negative impact on the environment but the methods themselves are expensive and consume a tremendous amount of electrical energy in the process of co-crystal formation. These methods don't utilize any organic solvents or harmful chemicals but it consumes high energy and require skillful operator for the formulation of co-crystals.

Another major challenge of co-crystals formulation is to confirm the synthesis of co-crystals. Mostly PXRD and single-crystal XRD are used to confirm the synthesis. But it is a bit expensive, so it's a need of the hour to identify a method that possesses more sensitivity and precision to primarily screen the effective coformer candidates for the particular drug. Thinking of this, it is also possible to screen promising coformer candidates by differential scanning calorimetry and it gives reliable results in most cases. But this method also has some limitations when API and coformer have the same melting point then it is difficult to almost impossible to differentiate between the DSC thermogram of individual candidates and co-crystals. It is necessary to develop a less expensive method to confirm the synthesis of co-crystals, which can help to identify the possibility of co-crystal synthesis.

Quantification of co-crystals in the final product is quite not possible with any conventional methods. With the help of Raman spectroscopy, it is possible to check the presence of unreacted materials in the final product, and with NMR spectroscopy one can accurately determine the bonds involved in the cocrystallization of two molecules. These advancements are showing promising results in the identification of cocrystals and also can replace the X-ray diffraction methods in the future. Here, Raman spectroscopy has

proven to be a better alternative as compared to NMR spectroscopy due to its ease of use and ease of interpretation.

There are major chances that co-crystals will hold popularity and have potential like salts in markets shortly. Co-crystals show better physicochemical properties like compressibility, flowability & hygroscopicity, and improved stability of drug than salt form, probably due to their stable crystalline form. Another reason for its increased craze of use is its patentability, which provides researchers and developers special access and ownership of molecules. With co-crystallization, it is also possible to utilize the old drugs more effectively for the betterment of the healthcare sector.

CRediT authorship contribution statement

Dhruv C. Sakhiya: Writing – review & editing, Software, Conceptualization. **Chetan H. Borkhataria:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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